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OVERVIEW OF AORTOCORONARY BYPASS GRAFTING FOR THE TREATMENT OF CORONARY ARTERY DISEASE: AN INTERNIST'S PERSPECTIVE

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OVERVIEW OF AORTOCORONARY BYPASS GRAFTING FOR THE TREATMENT OF CORONARY ARTERY DISEASE: AN INTERNIST'S PERSPECTIVE

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PREFACE

Medical technologies pose many complex and interrelated issues--for the health care professions, for patients, and for society. To help address these considerations, Congress established the National Center for Health Care Technology to conduct and sponsor assessments of health care technologies. Public Law 95-623 (the Health Services Research, Health Statistics, and Health Care Technology Act of 1978), which created the Center, defines health care technology broadly to include any means to prevent, diagnose, or treat disease or promote health. Furthermore, it calls for evaluation not only for safety and efficacy, but also for the social, ethical, and economic implications of technologies.

To provide medical and scientific background on certain selected technologies generally considered to be of particular significance, the Center has commissioned a series of overview papers, one of which follows. These were written by one or more authorities and are designed to review that state-of-the-art and identify, but not resolve, the key issues surrounding the subject. They are not intended to be comprehensive surveys of the literature. Each paper has been subjected to review by appropriate medical specialty societies, government agencies, and individual experts, and have been revised accordingly.

These overviews have been written for the general practitioner who may find information on a particular technology of assistance in his or her clinical work; they also may provide valuable background for assessments undertaken by the Center and for exploring the broad societal implications of health care technologies.

It is our hope that you will find the paper that follows interesting and useful.

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A HISTORY OF AORTOCORONARY BYPASS GRAFTING

For at least half a century we have understood that "the organization of medicine is not a thing apart which can be subjected to study in isolation. It is an aspect of the culture whose arrangements are inseparable from the general organization of society."(1) Therefore, to appreciate the widespread use of aortocoronary bypass grafting (ACBG) in this country to treat coronary heart disease, one must consider the changes that have occurred since the turn of the century in both people's lifestyles and in the practice of medicine.

Although angina pectoris was described by Heberden in 1768, it was not until 1912 that Chicago physician J.B. Herrick reported the diagnosis of the first myocardial infarction in a living patient. (2,3) Over the next three to four decades, the clinical manifestations of coronary atheorsclerosis were recognized with increasing frequency. By 1950, arteriosclerotic heart disease was the major cause of death in this country, accounting for 185.2 deaths per 100,000 population; this figure continued to rise until 1963, when the age adjusted death rate was 220.3 per 100,000 population. Approximately 50% of these deaths occurred suddenly, within an hour after the onset of symptoms. Despite the skepticism of a few, general agreement now exists that the increase in the death rate from ischemic (coronary) heart disease to epidemic proportions was a real phenomenon, and neither a spurious reflection of better diagnostic acumen nor a statistical illusion.

From the days of its earliest recognition, acute myocardial infarction created a sense of uneasiness in the mind of the attending physician. Herrick, in his initial description, emphasized "the resemblance of some of the cases to surgical accidents. The sudden onset of nausea and vomiting.... In my first case, while the diagnosis was that of a cardiac accident, there were so many disquieting features that surgical consultation was called to make sure that some surgical accident had not been overlooked."(3)

Despite increasing experience, the practicing physician did not appear to gain knowledge of the clinical manifestations of, or confidence in the management of, ischemic heart disease. The Seventh Edition of Cecil's Textbook of Medicine,

published in 1947, devoted only 6½ pages to the entire discussion of myocardial infarction and only ten pages to the entire subject of coronary artery disease.(4) In contrast, seven pages were devoted to pellagra and 29 to syphilis. The reader was advised that during convalescence from acute myocardial infarction, "after the third week has passed, the patient may begin to feed himself, may turn in bed without help, may have occasional visitors..." The section ended with the advice that "throughout the entire course every effort should be made to maintain high morale and an optimistic attitude on the part of the patient, and prevent venous thrombosis of the legs."

As the midpoint of the century passed, Levine and Lown, observing that the cardiac output was less in the sitting than in the supine subject, proposed the chair treatment for patients with acute myocardial infarction. But they were careful to recommend that two robust orderlies life the patient from the bed to the chair.(5) It is noteworthy that Levine warned physicians that "no one is blamed if the coronary patient died in bed; but if he had been out of bed, the physician is likely to be held responsible."(6) With the practice of such cautious and almost inept care, it was not surprising that surgeons developed an increasing interest in therapeutic efforts for these patients. In the early 1930s, Beck introduced the era of myocardial revascularization by initiating the first of a series of operative procedures to which as many as 20,000 patients over the next 35 to 40 years were subjected for the purpose of reducing pain, mortality, and/or premature death. (7) Few envisioned that such token efforts would lead to some 350,000 operations during the first decade of experience with ACBG.

After reviewing the successive acceptance and rejection of the numerous cardiovascular operative procedures which led to ACBG, Preston concluded that "the evolution of today's operation resulted less from the acknowledged failure of its predecessor than to the development of new surgical techniques and instrumentation that made each successive step possible. With the exception of internal mammary artery ligation, which in its simplicity was alone of all of the procedures prone to careful scrutiny, each operation lingered until replaced because of enthusiasm for a newer operation or modification that used more sophisticated surgical techniques."(8)

Both Cobb et. al. and Dimond et. al. compared the results of internal mammary artery ligation with those of a sham procedure. (9,10) In both studies the sham-operated patients had a "better result" than patients who received the "proper" operation. Dimond et. al. concluded that "the frightened, poorly-informed man with angina, winding himself tighter and tighter, sensitizing himself to every twinge of discomfort, who then comes into the environment of the great medical center and comes in contact with a powerful positive personality and sees and hears the results to be anticipated from the suggested therapy, is not the same total patient who leaves the institution with the trademark scar." It would appear that the success of such an operative procedure, regardless of its nature, is in part insured, for as Mundth and Austin pointed out, a patient who has had surgery is reluctant "after operation to reveal that he has persistent angina."(11)

The importance of these studies in contributing to the maturation of the science of medicine was emphasized by Beecher, who studied extensively the placebo effects of surgery in treating pain.(12) He concluded that "there is evidence in surgery, as in other fields, that the enthusiast gets results that are actually better than those of the skeptic. There are data to indicate that one can, and surgeons must, test their new procedures when value judgments are involved, so as to eliminate the effects of bias in their conclusions. The short life cycle (two years in this country from enthusiastic acceptance to discredit) of the treatment of angina pectoris by internal mammary ligation demonstrated how swiftly the proper design of study can answer difficult questions about the value of the procedure."

Finally, in 1968 Favaloro and his associates at the Cleveland Clinic demonstrated that ACBG could be performed with a low operative mortality and a high incidence of relief of pain.(13) This new operation was possible only because of the earlier development, also at the Cleveland Clinic, of selective coronary artery visualization by Sones and Shirey.(14)

When postoperative studies demonstrated that grafts bypassed significant obstructions and perfused ischemic or potentially ischemic myocardium, enthusiasm for ACBG mounted. Scientific skepticism and inquisitiveness were frequently abandoned as surgeons and cardiologists alike became impressed with early clinical

benefits. As previously indicated, some 350,000 patients were operated on during the first decade of experience with ACBG. Only 1,248 patients, however, were studied in a randomized manner, with half being delegated to surgery and half to no surgery.(15)

New knowledge regarding coronary heart disease was generated in many other areas. It became clear that the disease was not the result of an inevitable aging process but rather an epidemic disease resulting, at least in part, from the confluence of social pressures or forces identified as risk factors. These items included a rich diet resulting in elevated cholesterol levels and obesity, cigarette smoking, hypertension, and possibly sedentary living.(16) As knowledge regarding the genesis of coronary heart disease was revealed, new modes of medical management developed. The first coronary care unit was organized by Day in Kansas City in 1962.(17) Lidocaine and other effective antiarrhythmic agents were introduced, as were propranolol and potent diuretics such as furosemide. Furthermore, pre-hospital care and life support units became widely available.

Increasing numbers of patients with coronary heart disease were studied by selective coronary arteriography and ventriculography and investigators found that the prognosis of the disease was correlated with the extent of the atherosclerotic process as reflected by the number of vessels involved, the state of the contractility of the ventricle, and other parameters. Efforts were made to categorize patients with acute myocardial infarctions as good or poor risks shortly after admission to the cardiac care unit (CCU). Expansion of knowledge led to the replacement of pessimism by therapeutic optimism. These changes, although undoubtedly inevitable, were accelerated by the development of the Myocardial Infarction Research Units (MIRU) and Special Centers for Research in Myocardial Infarction (SCOR) sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

Reflecting these changes, the Fourteenth Edition of Cecil's Textbook of Medicine, published in 1975, devoted nearly 30 pages to coronary heart disease; it is interesting to note that two rather than seven pages were devoted to pellagra and 14 rather than 29 to syphilis.(18)

Many physicians became more aggressive in the management of coronary heart disease. The wonders of the CCU and the operating suite were described, if not glamorized, for the public and the profession on television, in the press, and at professional meetings. Many physicians came to believe that the activist or aggressive approach to patient management was more satisfying not only to themselves, but to the patient and his family as well. In many regards, the activist approach is more comforting to the physician. When severe complications or death occur, the activist can say: "We did everything that could have been done." The moment that invasive techniques and/or surgery are considered, decision-making becomes a shared responsibility, and as society becomes more litigious, such a realization is indeed comforting.

As a result of these changes, the number of options for treating patients with coronary heart disease greatly expanded. Nonetheless, the influence of each on the basic course of the disease remained incompletely understood. The responsibility of the physicion treating an individual patient with coronary heart disease appeared to have become more complicated.

Concomitant with, if not actually resulting from, the expanding base of knowledge and therapeutic efforts was a gratifying decline in the incidence of death from coronary heart disease.(19) The decline appears to have begun in the mid-1960s, but it may have started sooner in certain areas of the country, especially among white women. Since 1968, the downward trend has encompassed men and women, whites and blacks, and all adult ages, with the overall rate of decline being greatest among black women. If the death rates recorded in 1968 still existed in 1977 when the population of the country was larger and older, 630,000 additional deaths would have occurred between 1968 and 1976; 191,500 additional deaths would have occurred in 1977 alone. During this period, the death rate for coronary artery disease has increased in other countries except Australia, Belgium, Ca ada, and perhaps England, Finland, Israel and Japan. The decline, if any, in the incidence in these countries is small compared to that in the United States.

A recent report by the Metropolitan Life Insurance Company indicates that the degree of decline in mortality apparently varies among socioeconomic strata in our society.(20) Mortality has decreased more among urban, predominantly white, middle-

class males than among non-whites in lower socioeconomic strata. From 1969 to 1977, age-adjusted death rates from cardiovascular disease among white men in the general population fell 19%, from 459 to 367 per 100,000 population; among insured men, the decline was 31%, from 387 to 296 per 100,000 population. In 1969, the mortality rate among insured men was 18% lower than among white males in the general population, but by 1977 the difference had reached 37%. During the same period, the death rates declined 24% and 26%, respectively, among white women in the general and in the insured populations.

The cause of decline is uncertain. Although primary prevention through changes in risk factors, as well as better medical care made possible by fundamental and clinical research probably have contributed, they do not fully explain the decline. The relatively widespread use of ACBG appears to have had little influence on this trend. Stern concluded that even according to the most generous assumptions, surgery could not have contributed more than 4% to 5% to the total salvage of life.(21)

It was against this background that a logarithmic increase in surgical programs and numbers of surgically treated patients occurred. Braunwald expressed a growing sense of caution in stating that an industry was being built around ACBG: "the creation of the facilities for open-heart operations in community hospitals in which no other cardiac procedures are performed and the enlargement of surgical facilities in teaching hospitals, the proliferation of catheterization and angiography suites, as well as facilities for performing screening exercise electrocardiograms; and the expansion and development of training opportunities in clinical cardiology, cardiovascular surgery and cardiovascular radiology. This rapidly growing enterprise is developing a momentum and constitutency of its own."(22)

Such observations are cause for concern, for there are data to support the view that some doctors may create their own market.(23) The popular appeal of dramatic surgical intervention in a potentially fatal disease and the sense of insecurity that comes from withholding a major therapeutic alternative are exerting forceful pressures to establish ACBG as a conventional standard, although at the time of this writing findings with regard to this procedure's ability to prevent premature death are inconclusive except in selected subsets of patients.

It can be predicted that the next edition of Cecil's Textbook of Medicine will devote many more than 30 pages to coronary artery disease. Of the many new subjects that will be discussed at length, one almost certainly will be ACBG, which since the last edition was published certainly has become established as a major addition to the treatment of coronary heart disease. But one might question the wisdom of establishing with any degree of finality any form of therapy for patients with coronary heart disease at this time. The natural history of the disease is changing dramatically, and the incidence of death from it is declining in this country at an accelerated rate. Also noteworthy, and of considerable importance, are observations suggesting that spasm may play a role in the clinical manifestations of coronary artery disease and be modified by calcium flux inhabitation.(24) Such preliminary findings suggest that many time-honored assumptions about the pathophysiology of coronary heart disease may have to be changed. It would seem prudent for the physician to keep an open mind...and wait and see.

THE UTILIZATION OF ACBG

Introduction

This section will review selected published reports of the use of ACBG. Although technical considerations will be discussed, major attention will be directed to scientific and philosophical considerations important to patient selection. Such emphasis is reasonable, for since the publication of a previous review of the first decade of experience with ACBG, it has been adequately demonstrated that the procedure can be successfully carried out by many surgeons with a low operative mortality in most types of patients; such results are possible even in patients with acute myocardial infarction.(15,26-28) The probability that there may be wide variability in the technical execution of the procedure and, therefore, in the end results will be emphasized. It would appear that in considering the use of ACBG, it is no longer as much a question of "can you?" as it is a question of "should you?"

An effort will be made to identify the areas where general agreement on the use of ACBG exists. Attention will also be directed to what is not known or only partially known about the procedure, and about the disease process it is intended to counter. When areas of controversy are identified, effort will be made to present the differing views; such discussion may stimulate the initiation of well-designed, innovative investigations of the problem. But I wish to emphasize that considerable evidence, both scientific and anecdotal, indicates that ACBG is highly successful in a large percent of patients in relieving, at least for a time, the pain of refractory angina pectoris to acceptable medical management, and that such a demonstrated improvement in the quality of life for large segments of the population is sufficient to establish the procedure as a useful and clinically necessary part of the therapeutic armamentarium.

Technical Considerations

Technical considerations, including operative mortality, perioperative myocardial infarction, graft patency, and progression of disease in the native circulation will be reviewed before the selection of patients for ACBG is discussed.

Such an approach appears reasonable because of the tendency in some centers to recommend ACBG for asymptomatic patients and/or patients who might be expected to have a good prognosis without surgery. Before such practice is condoned, if indeed it should be, the possibility that surgery may be of limited or no benefit, or may even be harmful, should be thoughtfully reviewed.

Operative Mortality

In 1967, Favaloro demonstrated that a saphenous vein graft could be anastomosed to a partially or totally obstructed coronary artery and remain patent in the long term.(13,28) Furthermore, he and his associates demonstrated that the procedure could be carried out in large numbers of patients without inordinately high operative mortality. Based on the experience of their first 749 patients, they reported an operative mortality of 3.9% for single grafts and 9.8% for double grafts.(28) Since then, there has been a striking and gratifying reduction in mortality.(15, 26, 29-33)

Not surprisingly operative mortality has been reported to have decreased as surgical teams gained experience. At the Texas Heart Institute, the mortality from ACBG was 9.8% for the first 179 patients, 6.8% for the next 738 patients and 3.2% for the next 188 patients.(9) That operative mortality has varied among institutions is likewise not surprising. Such variability was a major point of discussion in the exhaustive criticism of the Randomized Veterans Administration Cooperative Study of Chronic Stable Angina.(34-38)

Operative mortality depends not only on differences in surgical skills, but also on patient selection. In a series of 699 patients who underwent elective ACBG only, Conley, et. al. observed a decline in mortality from 8.8% before January 1, 1972 to 5.4% thereafter.(39) This decline was associated with a two-to-threefold decrease in the prevalence of left ventricular dysfunction in the patients selected for surgery; within carefully described subgroups of patients, the operative mortality remained the same. Some series may contain large proportions of patients with few or even no symptoms or patients who are destined to do well with almost any form of therapy.

Furthermore, there is no universally accepted definition of operative death.(40) Some groups report operative mortality only when death occurs in the operating room, others include all hospital deaths, and still others define specific periods extending, for example, up to 30 days after the surgical procedure.

Operative mortality has been reported to increase with advanced age, and to be about four times higher in women than in men.(21, 22, 41-43) Why the latter is so, if indeed it is, is not altogether clear, although it may be women tend to be older than men at the time of surgery. Furthermore, they have relatively smaller coronary vessels, and it is more difficult to anastomose a vein graft to a small artery.(44) According to the Framingham study, women die more often from the first myocardial infarction than do men. Nonetheless, despite the initial sex difference in mortality, the late result appears to be equal in both sexes.(42, 43)

Operative mortality also has been reported to vary with the magnitude of the surgical procedure. Among the nearly 7,000 patients who received an ACBG at the Cleveland Clinic during its first seven years of experience, operative mortality was 0.8% for patients undergoing single, 1.4% for those undergoing double, and 2.7% for those undergoing multiple bypass.(33) These results are not surprising, for the number of grafts and the complexity of the procedure would be expected to reflect the extent and prognosis of the disease.

Most authors report a significant increase in operative mortality in patients having evidence of poor left ventricular performance.(15, 45-47) Kay correlated the surgical mortality of a group of 839 patients with the ejection fraction: 3% of patients with ejection fractions of 0.4 to 0.7, compared to 6% of those with ejection fractions between 0.25 and 0.40, died postoperatively. Surgical mortality was further increased in patients with congestive heart failure or cardiogenic shock and when the procedure was performed in conjunction with an aneurysmectomy or valve replacement.(47-56) Yet operative mortality was apparently surprisingly low under some circumstances of major impairment of ventricular function, i.e., an acute myocardial infarction or ischemia continuing after an acute myocardial infarction. Phillips, et. al., had an

operative mortality of 1.3% for 75 patients with evolving myocardial infarctions operated on within an average of 6.5 hours of onset of pain; Levine, et. al., reported an operative mortality of 8.8% in 80 patients who had sustained an acute myocardial infarction and experienced continuing unstable angina resistant to intensive medical therapy.(27, 57) Three of the seven deaths in the latter series were said to be noncardiac in nature.

In general, experience with ACBG over the last decade indicates that for carefully selected and skillfully managed patients, the operative mortality in many centers is extremely low--in some series nonexistent! For example, Kirklin and associates at Alabama reported a single hospital death among 551 patients between the ages of 50 to 70 years who were operated on consecutively.(58) Loop and associates at the Cleveland Clinic reported a 0.9% overall mortality rate from 1971 through 1978.(59) These remarkable results were attained despite increases in the median age of the operated population, the number of patients with multivessel disease and evidence of left ventricular asynergy, and the average number of grafts applied. Over an eight-year period, Tyras, et. al., at St. Louis operated on 184 patients with symptomatic single-vessel disease without a single operative death.(60) It can be concluded that, at least in some centers, the conditions that appeared to increase mortality during the earlier experience with ACBG can be overcome, and that operative mortality can indeed become almost nonexistent.

At centers where such low operative mortality is consistently attained, the physician need not hesitate to recommend surgery for fear of high surgical mortality. He can identify those patients who, based on currently-available knowledge, "judgement," and/or clinical experience, have poor prognoses, and with a high degree of confidence make decisions regarding surgery accordingly. The importance of this issue was emphasized by Hurst, et. al.(26) The Emory Group reported that in their institution, "the overall operative mortaity was about 1%. The operative risk in certain subsets of patients with CHD is about 0.5%." They concluded that "these operative results make it possible for us to recommend surgical treatment in certain patients whereas we would not recommend surgery for the same patients if the operative risk was 5%."

But in not all institutions in this country do patients enjoy an operative risk equal to that reported by Hurst, et. al.(26) As previously stated, operative mortality varies

from institution to institution. Richter, et. al., found that the operative mortality associated with ten separate surgical teams in a large metropolitan area varied widely according to both the surgical group and the hospital involved.(61) In no group in this study was the operative mortality influenced by the year in which the surgery was done. Furthermore, Chalmers, et. al., found that the case fatality rate in 16 hospitals in the New York metropolitan area in 1976 varied from 0% to 14%, with a mean of 5.64%.(62) This mean exceeded that of 21 series reported in the literature in 1977 (range 1% to 10%, mean 3.98%). These differences in operative mortality are not surprising in view of the foregoing considerations and the extent of differences in opinions regarding major technical elements of the procedure and in the experience of surgeons performing ACBG.(63, 64)

It should be noted that since the report by Chalmers, et. al., Griffiths, et. al., reported that the operative mortality for ACBG in the entire state of New York was less than 3% in 1977, as opposed to 8% in 1970.(62, 63) Griffiths, et. al. further described a system whereby cardiac diagnostic and surgical services were approved and monitored by a Cardiac Advisory Committee to the New York State Commissioner of Health.(63) The mortality figures embrace 29 hospitals performing ACBG. Undoubtedly, some hospitals and surgeons have operative mortalities greater than the published average, and some less. Therefore, even with such a system, the mortality in some hospitals could at least temporarily exceed the 5% figure cited by Hurst, which creates difficulty.

These considerations are of utmost importance to the vast majority of patients undergoing ACBG in this country and to the clinicians recommending surgery for such patients. Most patients do not receive their medical care, and many do not receive their ACBGs, in teaching institutions or hospitals in the habit of reporting their results in the literature. These people receive their care in community hospitals. Poor results are rarely reported. On the other hand, many physicians do not report outstandingly good results. With these and other considerations in mind, Motulsky postulated that surgical results as reported in the literature tend to be biased towards the positive side.(65) He observed that, "'Occasional' surgeons are less likely to present their results than surgeons at academic centers. Morbidity, mortality and outcome reported

from surgical centers tend to be more favorable than those of 'occasional' surgeons whose experience is unrecorded. The 'average' patient, therefore, probably has a worse prognosis with a given operation than that reported in the surgical literature." Therefore, factors that appear to have increased mortality in the past may continue to be a cause for concern in patient selection for segments of our society.(30, 33-39 41-57)

For ACBG to be recommended for the majority of "average" patients with coronary heart disease, especially those who are asymptomatic, it would appear that information regarding the mortality in the "average" hospital in this country is needed. The clinician practicing remote from a medical center that critically analyzes and reports its results should be encouraged to be critical of his own results and those of his peers and to demand knowledge of performance before making decisions regarding ACBG, especially when the procedure is elective. Although these comments appear critical of community hospitals, they are not intended to be so, nor to imply that patients cannot get good, or in many cases superior, care in the hospital close to home. It is well known that the morbidity and mortality for ACBG are high even in some university hospitals. The questions surrounding the choosing of this procedure emphasize a current and chronic dilemma of the patient, and in many cases the clinician, dealing with the health care system, namely: to find out how good or how bad the care is in a given hospital or physician's service or office.

Perioperative Myocardial Infarction

Previous reviews of the results of ACBG have indicated that perioperative myocardial infarctions occurred in about 10% to 15% of all operated patients, with rates in individual series ranging from 1.3% to 40%.(15, 33, 46, 66-73, 11) The frequency of the diagnosis appears to depend not only on the clinical condition of the patient at the time of surgery, the technical skill of the operating team (including the anesthesiologist), and the design of procedures and techniques intended to support the myocardium, but also on the diligence with which evidence of perioperative myocardial damage is sought. Reliance solely on the appearance of new Q waves on the postoperative ECG as evidence of a myocardial infarction grossly underestimates the occurrence of perioperative injury, for as Assad-Morell, et. al. reported, only 5 of 14 patients dying postoperatively and demonstrating acute myocardial infarction at

autopsy had ECG changes indicative of the injury.(74) Most investigators now use serial isoenzyme measurements and/or radionuclide imaging in addition to the ECG to determine if injury has occurred.(75-83)

Despite what might be expected, graft occlusion did not appear to be the major cause of perioperative myocardial infarction. Postoperative angiographic studies in patients with evidence of perioperative myocardial infarction have shown higher but statistically insignificant incidence of graft occlusion, new total occlusion of the corresponding artery, and decrease in normal wall motion of the corresponding myocardial segment.(74,84) A decline in ejection fraction accompanied such changes.(85) In a postmortem analysis of 58 patients who died within one month of ACBG, Bulkley and Hutchins found that only 4 of 18 patients demonstrated regional transmural necrosis that could be attributed to newly-occluded bypassed vessels.(86) The distribution and distinctive histologic findings of contraction band necrosis suggest that most perioperative infarctions are related to reperfusion through widely patent grafts after a period of nonperfusion during operation.

Based on these and other considerations, a number of modifications of various aspects of the surgical procedure were introduced to preserve the myocardium. The results have been gratifying, at least in the experience of the reporting groups. These measures include cross clamping and profound regional hypothermia, atrial venting, avoidance of electrical fibrillation of the heart, use of magnifying lenses, potassium cardioplegia at 4°C, intracoronary shunting limiting the coronary occlusion during graft constriction to a few minutes, and continuation of the administration of propranolol until just before surgery with its prompt reinstitution after surgery.(77, 87-92) Feola, et. al. reported that the use of intra-aortic balloon counterpulsation, instituted perioperatively and continued postoperatively, was associated with a reduction of perioperative myocardial infarction from 30.4% to 4% in patients with poor left ventricular function (ejection fraction less than 0.30).(93) Because, or perhaps in spite of, compulsive attention to details such as those cited above, many groups are now reporting perioperative myocardial infarction rates of 0% to 6%.(26, 31, 59, 60, 88-94)

Such results are indeed gratifying. Regardless of earlier reports suggesting that a perioperative myocardial infarction is well tolerated, ample evidence indicates that

patients with this perioperative complication have increased incidences of ventricular arrhythmias and of late death.(95, 97, 73, 74, 84) Furthermore, myocardial infarction is considered the cause of most immediate surgical deaths and is associated with almost all deaths in the 30 days following surgery.(98, 99)

The same concerns that were raised regarding operative mortality in institutions that do not report their work in journals can be voiced regarding the incidence of perioperative myocardial infarctions. The incidence of perioperative myocardial infarction in the country-at-large is probably greater than that reported in the literature, not only for reasons similar to those noted for operative mortality, but also because of the difficulty in making such a diagnosis based on the ECG alone. Many hospitals do not routinely analyze the blood for changes in levels of isoenzymes and do not use radionuclide imaging. The referring clinician must know the experience and "quality of the surgery" of the consulting surgeon if the patient is to avoid the risk of unnecessary injury to the myocardium.

Long Term Graft Patency

The durability of the vein bypass conduit is essential to a successful ACBG. Along with the operative mortality and perioperative myocardial infarction rates, it is an index of the "quality of surgery."

Most studies performed relatively soon after surgery have demonstrated a close correlation between graft patency and improvement of clinical symptoms, exercise capacity, and ventricular function.(15, 33, 66, 100-104) A few investigators, however, have reported clinical benefit from ACBG despite closure of most or all grafts.(67, 75, 105-107) Mintz, et. al. recently reported observations of sequential studies of left ventricular (LV) performance and segmental wall motion one week, two months, and during the first year postoperatively.(108) They found that the ejection fraction was significantly lower in the early postoperative studies than longer after surgery. This difference may result from the higher heart rate during convalescence than afterwards (91 ± 2 vs. 69 ± 4 beats/min). These investigators concluded that observations made at widely differing times during the early postoperative period should not be pooled in determining operative results; about two months are required for the symphony of

reflexes that might have been deranged by surgery to become synchronized. Particularly noteworthy was the demonstration by these investigators that, of seven patients who had a preoperative myocardial infarction, five showed improved segmental shortening in the distribution of the graft to the infarcted area two months postoperatively. This observation suggests that reperfusion of ischemic muscle in and around areas of prior infarction can improve regional contraction there.

Improved left ventricular function has been demonstrated for as long as five years after surgery, and appears to correlate with graft patency. Tyras, et. al., restudied angiographically, at least five years after operation, 181 of 531 patients who underwent ACBG during 1970 -- 1973.(109) Five patterns of postoperative ventricular function were identified: abnormal LV function improving to normal LV function; unchanged normal LV function; abnormal LV function improved but not normal; unchanged abnormal LV function, and deterioration of LV function. Forty-nine percent of the series regained (40 patients) or retained (40 patients) normal ventricular function; 20% experienced deterioration of ventricular function. Graft patency and relief of angina were said to be significantly better in those patients who maintained or attained normal LV function than in those in whom LV function deteriorated. These data suggest that five years after surgery, one-quarter of the patients will maintain previously existing normal ventricular function; one-quarter, who had abnormal LV function, will regain normal function; in one-quarter, LV function will not change or will improve but not become normal; and in about one-fifth (20%) LV function will worsen.

The graft patency rates reported in the literature have varied widely. Recent reports from centers with considerable experience tend to be superior to those performed earlier in the 1970s. Investigators in the often-criticized Randomized VA Cooperative Study of Stable Angina reported that 69% of all grafts were patent one year after operation and 88% of the surgical patients studied had at least one patent graft.(34) In the Randomized VA Cooperative Study of Disease of the Left Main Coronary Artery, Takaro, et. al. found that 69% of the grafts were also patent one year after surgery.(110) Guinn and Mathur reported an overall patency rate of 77% from a randomized study of stable angina conducted solely in the Houston VA Hospital.(111) At first glance the rates of graft patency in these three randomized studies might appear inferior to those in larger, nonrandomized studies such as those conducted at about the

same time by Loop, et. al. and Lawrie, et. al., since both of the latter groups reported a long-term patency rate of 87%.(37, 115) Nonetheless, it should be appreciated that the former and latter studies had markedly different protocols and evaluated widely different percentages of the total number of patients operated. In the three randomized VA-based studies, 94.4%, 72.7% and 87.6% respectively of the patients who survived one year operation were examined radiographically.(34, 110, 114) On the other hand, Lawrie et. al. studied only 15.3% of the patients, and the interval after operation ranged from 0 to 75 months, Loop and his associates reported the results of studies performed up to 50 months after surgery on approximately 43.9% of the patients.(112, 37)

When patients are studied in a nonsystematic way, various biases can be introduced. For example, a disproportionate number of patients with only a single graft may be studied.(33, 113) When only one graft is needed, it is most frequently of the left anterior descending coronary artery, and a higher patency rate of graft to that artery than to the other two arteries have been reported.(114) In the absence of a restricting protocol, the same grafts may be studied and counted as patent more than once; grafts demonstrated at autopsy to be patent may be included in the total number.(115, 118) Finally, studies may be performed by a number of different individuals and groups in referring hospitals, where commitment to the quality of data-gathering may vary.(35)

In3order to avoid such biases, at least two groups attempted to study repeatedly a large percentage of all patients who were operated on. Fitzgibbons, et. al. opacified, 1,400 grafts in 409 survivors of 414 consecutive operations before hospital discharge.(116) Eighty-one percent of the grafts in the living patients were studied again within one year after operation by precisely the same technique. In this large, nearly consecutive series of patients, 19% of the grafts were demonstrated to be occluded within the first postoperative year.

Grondin, et. al. examined the status of 155 grafts in 106 patients operated on nearly consecutively, at least two weeks, one year, and three years after surgery.(117) Each phase of the study was conducted in more than 90% of the patients who survived and who had had a patent graft demonstrated previously. Thus, three years after surgery, 75.5% of all grafts implanted had been visualized three times or were known to be

occluaed. These investigators reported that the graft occlusion rate was 11.3% by two weeks, 20% from two weeks to one year, and 5.1% from one to three years. In this study, of 117 grafts whose fate was known, 35.7% were occluded three years after surgery.

These investigators then compared patency in the patients initially undergoing ACBG with those operated on after two years of experience.(118) The "early" group of the Montreal Heart Institute consisted of 124 of the first 138 patients who were operated on from September, 1969, to October, 1970. The "late" group included 83 of the 100 consecutive patients operated on between November, 1971 and July, 1972; by that time, "modification of surgical techniques" had occurred. Patients in both groups were studied two weeks and one year after surgery. The authors emphasized that the groups were clinically similar; the only difference was "increased experience of the surgical team, surgical techniques and probably skill." Various combinations of grafts to multiple coronary arteries were performed in many of the patients in the "late" but not the "early" group. The patency rate at two weeks did not differ significantly between the two groups: 86.3 versus 91.8%. However, proportion of grafts showing significant stenosis at anastomotic sites decreased markedly: 15% to 5.5% (P less than 0.025); and the patency rate at one year improved from 67% to 85.5% (P less than 0.0005). These observations and those of others indicate that increased operative experience results in increased graft patency.(59, 114)

In order to evaluate systematically long-term graft patency, the investigators at the Montreal Heart Institute combined the first 138 patients operated on in their hospital with 99 patients (Nos. 379 to 478) operated on after two years' experience.(119) From the total of 237 patients, 198 were selected because they survived and were found by angiography to have at least one patent graft 6 to 18 months after surgery. Ninety-eight of the 198 were excluded: 32 died before the time of study; 27 patients or their physicians refused permission to participate in the study; for 19, the study was considered unjustified because of medical reasons, of which severe peripheral vascular disease was the most frequent; 18 were lost to follow-up or were not available at the time of study; and seven patients had been reoperated on or had had a late study between 42 and 54 months. The remaining 100 patients, who constituted the study group, represented only 44% of the original cohort. These were found to have a total

of 159 patent grafts and an unstated number of occluded grafts. Only 17 of 159 grafts known to be patent one to 18 months after surgery were demonstrated to be occluded during the five-year interval.

Thus an average annual attrition rate of 2.1% after the first year was reported. The annual attrition rate was 2.4% for grafts placed during the earlier surgical experience, but 0.7% for those benefitting from two year's surgical experience (P less than 0.05). The investigators concluded that the "cumulative graft patency in the near-consecutive 'unselected patients' operated after two years of experience was 85.5% in the first year and 83.2% by five years." Actually, only 37 of 99 (38.3%) consecutive patients who were operated on after two years' surgical experience were studied.

At present, there is marked variability in the way that grafts are established: a single graft; a Y-graft; a sequential side-to-side graft; a sequential end-to-side graft; a low-flow graft; a high-flow graft; a graft to arteries that have diameters at least 1.5mm and free of atherosclerosis and lead to relatively large vascular beds; a graft to arteries without these desirable qualities; and so forth. The Grondin study included in its "late" series 88 single grafts, 49 sequential grafts to multiple coronary arteries, and 6 Y-grafts.(122) Further experience will be required to determine if long-term patency will be as good for each type of graft. In another paper, Grondin and Lemet stated that it is apparent that "certain combinations of side-to-side anastomosis and end-to-side anastomosis give better results than others."(120) Moreover, grafts with only one side-branch appear to fare better than those with multiple, side-to-side anastomoses. It should be emphasized, however, that these investigators reported a low attrition rate for entire grafts with sequential anastomosis. Of 44 grafts studied in 40 consecutive patients shortly after surgery, only one complete occlusion of the vein graft was demonstrated. When 27 of these patients were studied one year after surgery, none of the grafts was completely occluded.

Prediction of late patency of an ACBG clearly is desirable, yet thus far no single item has emerged as a valid predictor of patency. Factors that would appear to influence patency in individual patients, and that have been extensively studied, include the

particular vessel grafted, mean graft flow, response to drugs such as papaverine, the ratio of diastolic to systolic flow components of the cardiac cycle, the angiographic appearance of the host vessels, the reactive hyperemia flow response, and coronary vascular resistance.(125)

In addition to technical influences, patient factors such as smoking and elevated blood lipid levels can influence graft patency.(44, 126-132) The magnitude and uniformity of the influence is uncertain. Although coronary venous graft atherosclerosis has been observed, it appears to be uncommon. Most of the changes in grafts appear to relate to damaged endothelium, fibrin deposition, and a myoproliferative response. The resulting fibrous proliferation can rapidly lead to total occlusion of the graft. When such occurs, it usually does so within the first postoperative year. Most investigators have stated that the typical atherosclerotic plaque is extremely uncommon, if not nonexistent, before the second year.(44, 122-124, 131, 132) Nonetheless, Bulkley and Hutchins have reported early atheromatous changes within the first postoperative month.(125) Clearly, much remains to be learned about the changes that occur in the graft.

Unfortunately, most institutions do not study patients objectively to determine either long- or short-term patency. The selection of patients for study may well introduce bias; for example, in many institutions patients with symptoms are more likely to be studied because it has been suggested that they are more likely to have occluded grafts, and this contributes to an underestimation of the "true" level of graft patency. The above considerations would seem to imply under-, not over-, estimation. (36, 37, 15, 119).

Above all, the long-term benefits of ACBG depend on a high rate of long-term graft patency, and the patient contemplating surgery has the right to know the "true" patency rate obtained by his surgeon. Clearly, a noninvasive, easily executed method that will be readily adopted by community hospitals is sorely needed to determine graft patency periodically. The use of computed tomography, as recently described by Brundage, et. al. is encouraging in this regard.(128)

Acceleration of the Disease in the Native Circulation

In 1971, Aldridge and Trimble first reported that the addition of a vein conduit to a coronary artery accelerated the atherosclerotic process in the native circulation.(129) After examining their own material and pooling it with data reported from five other institutions, Griffith, et. al. confirmed the observation.(130-134) In 663 arteries with a patent graft, there were 264 (40%) new total occlusions, of which 85% were proximal to the anastomotic site. Two hundred eighty-one arteries had occluded grafts, and 119 new total occlusions (42%) of recipient arteries were demonstrated. Only 43 new occlusions (6%) were demonstrated in 726 arteries without grafts.

Subsequent observations have demonstrated that it is common for occlusions to occur at what would appear to be an accelerated rate proximal to the insertion of a graft, but uncommon for such an acceleration of disease to occur distal to properly placed grafts.(135, 136) For example, Frick, et. al. studied 214 grafted and 208 nongrafted arteries in 77 patients at a mean of three weeks and again at 13 months postoperatively.(136) The authors indicated that because of their philosophy of attempting to revascularize the heart completely, most of the nongrafted arteries at the completion of surgery were essentially normal. New lesions developed in 0.7% of the nongrafted, previously normal arteries; 7.6% of the nongrafted vessels with previous luminal obstruction showed evidence of progression. Progression of the disease occurred proximal to the graft insertion in 24.2% of the arteries and progressed to a total occlusion in almost 50% of these. Disease in the proximal segment of grafted arteries progressed to occlusion with equal frequency in association with patent and with occluded grafts. However, progression of disease distal to a graft insertion occurred in only 2 of 85 arteries, and in neither did it result in complete occlusion.

Mathur, et. al. found no "striking difference in the progression of disease" between randomized operated (18%) and nonoperated (11%) patients studied a mean of 24 months postoperatively.(137) He and his associates suggested that studies demonstrating significant progression of disease may have been biased by studying a disproportionate number of patients who volunteered for study because of symptoms. Ben-Zvi, et. al. reached the same conclusion.(138)

To date, one of the most carefully conducted studies of "progression of disease" is that of the Montreal Heart Institute. Bourassa, et. al. identified an original cohort of 500 consecutive patients operated on between September, 1969, and July, 1972.(139) Where possible, these patients were to be studied angiographically two weeks, one year, and six years following bypass surgery. In the spring of 1977, 389 of the original 500 patients were available for study (16 had been lost to follow-up; 11 were living in foreign countries, and 84 had died, 37 at operation). Of the potentially-available 389 patients, 281 were further excluded: 136 patients had not had the early postoperative or the one-year angiographic study; the study was unavailable or inadequate in five; all grafts were demonstrated to be occluded at the early or one-year study in 64; and 70 patients or their physicians refused further studies. Thus, of the original cohort of 500 consecutive patients, a study group of only 108 patients (21.6%) remained. All had had coronary arteriography one month after surgery and all but four one year after surgery. These 108 patients were again studied 72±10 months (54 to 91 months) after surgery. They had a total of 281 saphenous vein grafts, of which 158 were patent and 43 (22%) occluded.

At one year, grafted and nongrafted arteries differed markedly in progression rate. Only eight of 84 existing stenotic lesions (9.5%) in nongrafted arteries showed significant progression, and none of 25 normal vessels developed new lesions that stenosed the luminal diameter by more than 50%. In contrast, many of the grafted coronary arteries that obviously were stenosed preoperatively progressed markedly during the year following bypass surgery. Preexisting stenotic lesion increased in 60 of 106 (57%) proximal vessels with patent grafts and in 9 of 17 (53%) proximal arteries with occluded grafts. Ninety percent (54 of 60) of former and 78% (7 of 9) of latter grafts became totally occluded. Six years after surgery there was little evidence of further progression, for essentially all occludable proximal lesions were already occluded by the end of the first year. In contrast, disease progressed in only 7.3% (8 of 109) of nongrafted arteries studied at one year compared to 41% (46 of 113) of the vessels studied 72±10 months after surgery. Only 2.4% (5 of 201) of arteries distal to bypass grafts showed significant progression of obstructive disease. It is noteworthy that new lesions producing greater than 50% narrowing occurred in only 7% of previously normal arterial segments. Of 13 grade 1 or 2 (out of 5) narrowings of the left

main coronary artery, only three progressed to grade 3 stenotic lesions. Lesions obstructing the lumen less than 50% showed little tendency to progress, whereas those obstructing it more than 50% progressed rapidly. Whether left alone or bypassed, lesions producing between 50 to 75% obstruction showed the same degree of progression after an average of six years. Progression occurred within six years in one of two lesions with a greater than 75% occlusion of the lumen and almost invariably resulted in total occlusion.

Several investigators have cautioned against misinterpretation of "apparent" total occlusions of an arterial segment as demonstrated by coronary arteriography.(139-142) Functioning grafts transmit aortic pressure to the coronary segment distal to proximal narrowings. Thus, with widely patent grafts, the pressure gradient across the stenosis can be virtually eliminated. Flow across the stenosis is thereby reduced or eliminated, even in the absence of anatomic obstruction. Although such a phenomenon probably does occur, for a patent artery to masquerade as an occluded artery during carefully executed arteriography must be uncommon. But this same pressure gradient phenomenon appears to contribute to the development of the accelerated proximal occlusion. There is, evidence, however, that occlusion sometimes may result from surgical manipulation of the diseased artery.(136) A recent report of a pathologic study that found 17% of coronary arteries dissected at the site of the graft anastomosis supports this suggestion.(99)

Surveying the previously cited observations, investigators at the Montreal Heart Institute concluded that "previous concern that saphenous vein grafting will accelerate the process of coronary disease has relatively little long-term justification." It is unfortunate that the study embraced only 21.6% of the consecutively operated on patients and it is uncertain whether the experiences of this relatively small group represents that in the other 79.4%. Also unfortunately, other oft-quoted studies of the long-term efects of ACBG on native circulation appear to suffer from the same sources of potential bias.(143-145)

Before ACBG is further applied to large numbers of asymptomatic patients, carefully designed and executed studies appear to be indicated, although progression of disease in the native circulation as a result of surgery seems to be less of a problem than initial findings suggested.(15, 70, 129-133) Nevertheless, most studies do show that

coronary atherosclerosis does progress in the native circulation in both operated and nonoperated patients. For most, therefore, surgery is "not a pardon but rather a stay of execution." An active therapeutic program designed to minimize the progression of the atherosclerosis is thus in order, even in the operated patient.

ACBG IS BETTER THAN ... WHAT?

For a therapeutic measure to become validly established, it must be shown to relieve symptoms and improve the "quality of life" and/or increase the "quantity of life." These benefits must be accomplished without undue risks to the patient. Furthermore, they must be attainable within the limits of the economic resources available to the patient or society. To demonstrate such benefits, outcomes with and without the therapy must be compared. Thus, a control is needed. This chapter will discuss the difficulty of identifying a proper control against which to determine the ability of ACBG to postpone or prevent premature death.(123-148)

The most widely used controls have been the natural history studies of coronary heart disease conducted in earlier decades. These included patients followed after coronary arteriography for periods of three, five, or even ten years at the Johns Hopkins Hospital, the Cleveland Clinic, and other centers engaged in pioneering coronary arteriography.(146-152) These studies, in the judgement of many, are unacceptable controls for today's procedures because:

1) The patients lacked the benefits of current pharmacologic agents and understanding of the pathophysiology of the disease;

2) The patients were not exposed to current social pressures to modify risk factors;

3) Many of the patients were referred to the "reporting centers" because their disease was especially difficult to manage in their local communities, thus there were no, or few, essentially asymptomatic patients;

4) In a number of centers, patients were assigned to "medical programs" because they were not considered "ideal" for the surgical procedure of the day, i.e., internal mammary artery implantation. Thus, many of the patients might be considered the "surgical rejects" of the day;

5) Finally, when these patients returned to their local communities after angiographic studies, they usually received "no therapy" rather than the currently-practiced compulsory medical therapy incorporating both pharmacologic agents and behavioral modification. Proudfit quite properly pointed out that only one of the studies, that of Webster, et. al., was designed to address the question of surgical candidacy.(153, 149)

The second type of control population consists of concurrent medically treated patients matched to the surgical patients by a number of carefully defined and readily identifiable discriminating variables. These include age, sex, and behavioral characteristics, as well as anatomical findings, measurements of hemodynamic parameters, ventricular function, and so forth. By means of computer techniques, approximately 100 variables can be considered. Investigators at Duke University Medical Center have pioneered the application of these techniques to studies of ACBG.(20, 160) Many other investigators have applied similar methods but used a smaller number of discriminating variables.

A third control technique is the use of life tables of the population-at-large, with or without exclusion of patients with heart disease.(160, 169) This approach ignores the fact that a surgical group, particularly if treated in a private institution, comes from the more affluent and more highly motivated sector of society. Such patients do not suffer from the potential disease-producing stress of unemployment; they possess certain characteristics, despite their disease, of the "healthy worker."(157, 158)

Careful selection of patients for surgery excludes those who are morbidly obese, if not simply obese, who have florid tobacco bronchitis, who have debilitating or potentially debilitating diseases, are alcoholic, and so forth.(33) Many surgical patients stop smoking and control other known risk factors. Finally, the Metropolitan Life Insurance Company has recently reported that the decline in mortality observed in this country during the last two or more decades has been greater among urban, predominantly white, middle-class males, i.e., life insurance policy holders, than among persons in the lower socioeconomic, largely non-white strata of society.(20) Thus, it seems entirely possible that a carefully selected population of surgical patients could survive longer than the population-at-large regardless of surgery.

A fourth type of control is obtained by randomization.(34, 110, 114, 159, 161) This approach, when applied to ACBG, has generated much discussion. Some investigators believe that such a procedure should be subjected to randomized trials from the start, whereas others do not believe that surgeons can do their best work if they do not believe that "their approach is the best form of therapy."(35-38, 62, 162-168) This subject has been discussed exhaustively, and further attention is beyond the scope of this review.

A fifth approach is to use no controls and simply state that in the literature no nonsurgical group of patients with similar medical characteristics could be found that had done as well with nonoperative therapy as had those with the reported surgical therapy.(170)

Studies of the effect of ACBG on age at death can be classified according to which of the previously-mentioned five experimental designs were followed. The superiority of surgery seems more impressive in the reports of studies that compared the results to no controls, historical controls, the population-at-large, or to concurrent controls matched for only a few variables. The benefits of surgery are less striking, or not demonstrated at al, in studies that use concurrent controls matched by numerous variables and in prospective randomized studies. At the risk of oversimplification, it would appear that as a general rule, the more rigidly the control population is defined and matched with the surgical population, the less surgery contributes to postponing death; the less rigidly controlled the study, the better the apparent results of surgery. Chalmers, et. al., in defending the VA randomized control trial, reported similar conclusions after analyzing studies evaluating the use of stilbesterol in the prevention of spontaneous abortion, anticoagulants in myocardial infarction, both preventive and therapeutic shunts in cirrhosis, and gamma globulin for post-transfusion hepatitis.(62)

The suggestion that rigidly controlled studies do not demonstrate the benefit of surgery as frequently as less rigidly controlled studies does not exclude the possibility that surgery might postpone deaths in selected subsets of patients with coronary heart disease. Feinstein has pointed out that the selectivity of the admission process can mean that patients in a randomized or rigidly controlled study differ from those seen

in day-to-day practice in the community, or in medical centers, or even from the type of patient that the study was designed to evaluate.(168) Nevertheless, those who are admitted to the study are randomized, receive a specific treatment and are studied, and yield the results of the trial; those results are subsequently published and serve as a guide for treating patients like those who were initially supposed to have been studied.

Boncheck and Rimm implied that the randomized study reported by Kloster, et. al. might reflect a nonrepresentative spectrum of coronary heart disease.(162, 159) They stated that the "average cardiac mortality in the medically treated group was less than 5% per year which is, therefore, the maximal possible improvement in survival even with perfect operative results." Kloster's group replied that their patient population was representive and concluded that "it is unfortunate for those who set out to demonstrate improved survival with coronary artery bypass that current modes of medical management appear to have favorably altered the natural history of coronary disease." Gross, et. al. reported a similarly favorable survival rate for 231 patients rejected for ACBG between 1971 and 1974.(178) Fifty of their patients had suitable anatomy and LV function to warrant surgery; nine had three-vessel and 20 two-vessel disease, and 10 had isolated proximal left anterior descending stenosis. The remaining 11 had high-grade stenosis of the right coronary artery. There was only one death in a three year follow-up (97.9% three year survival).

As previously indicated, most medical care in this country is provided not in medical centers but in community hospitals. Motulsky reasoned that "patients with more severe symptoms are more likely to find their way to physicians. Asymptomatic patients are less likely to come to medical attention unless specific screening is performed, such as routine blood pressure readings for the detection of hypertension...those who are studied in medical centers will often have been referred by their private physicians and on the average will be more severely affected. More dramatic complications are more likely to be reported than is a course free of complications. Long-term prospective studies on the natural history of chronic disease are rarely performed in academic centers and are lacking for most disease. Thus, mildly affected patients are less likely to find their way into the medical literature."(65) These reflections are relevant consideration of the benefits of ACBG. There is ample evidence that the natural history of coronary heart disease has changed in this country.(171) The cause of

this decline has not been established with confidence, although the decline in mortality from coronary heart disease has paralleled decreases in prevalence of certain behavioral characteristics of this society, other changes clearly have occurred as well. The medical management of ischemic heart disease has been forcefully influenced by the introduction of new modes of therapy including coronary care units, life-support systems, and drugs such as lidocaine, propranolol, potent diuretics, and calcium antagonists.

The decline in mortality from coronary heart disease seen in the U.S. is visible in other, but not all, advanced societies. Barrett-Boyes recently emphasized the declining mortality from coronary heart disease in New Zealand in a report of the preliminary results of a randomized study of 87 male patients under the age of 60 years who had had two or more myocardial infarctions documented by enzyme rises, electrocardiographic changes, or both.(161) None of the randomized patients had more than mild angina. They all had significant coronary artery disease, and the "majority" had triple vessel disease. Patients with significant symptoms were placed in an elective surgical group and were operated on without randomization. Among the 45 medically treated patients, death occurred during an average of three to four years only in patients with an ejection fraction of less than 50%; i.e., no patient with a normal ejection fraction died during the study. The survival for the nonsurgical group was 87%, compared to 82% for the 42 surgical patients. Barrett-Boyes stated that after five years neither medical nor surgical management showed an advantage as regards either survival or subsequent myocardial infarction. He concluded that "the most striking finding of all was the excellent survival in the trial medical group." He further stated "that in patients with pain, [the] question of prolonged survival is really of secondary importance. The operation is indicated for the relief of symptoms, for which it is highly effective. However, the dilemma is vastly different when we are presented with a patient with severe coronary artery disease but no pain."

The dilemma of the asymptomatic patient is becoming increasingly more difficult with each passing year. More and more persons are requesting, or being referred by their physicians for, stress examinations as part of an annual physical examination, for employment in potentially hazardous occupations, or before beginning an exercise program. Some show a positive treadmill response despite the absence of symptoms, and such patients are frequently subjected to cardiac catheterization. Other patients

with chest pain, frequently atypical, but with no electrocardiographic changes even with stress, are referred to the catheter laboratory as well.* Significant coronary lesions may be demonstrated in both types of patients, and in many centers their prognosis based on the demonstrated lesions is stated. Unfortunately, the predicted prognosis for both types of patients is almost invariably based on the natural history of symptomatic patients studied over a decade ago, for there are no life table studies available solely for the natural history of "asymptomatic patients with coronary heart disease."(146-157) Selzer and Cohn recently discussed the fallacy of such prediction.(172) They pointed out that the early studies almost certainly embraced a spectrum ranging from patients with anginal pain as the only detectable abnormality to those with heart failure, cardiomegaly, extensive myocardial damage, or grossly abnormal electrocardiograms, with or without angina.

Philips and Mauter concluded that there is clearly a need to find a pathophysiologic "connecting link" between the symptoms and/or signs and angiographically demonstrated lesions of the coronary arteries.(172) "This lesson was well learned in reference to renovascular hypertension. Here the pathology was occlusive renal artery disease and the altered physiology was hypertension. The connecting link was the demonstration of excessive renin production from the abnormal kidney. This served accurately to predict which hypertensive individual would benefit from renal arterial corrective surgery."

The dilemma confronting cardiologists today is whether the time frame, i.e., the abscissa (in years) against which both symptomatic and asymptomatic patients treated in this decade will be plotted, is the same as that developed for the data collected before ACBG came into vogue.(146-152) Observations like those of Barrett-Boyes, Kloster, et. al., Mathur and Guinn, the NHLBI Unstable Angina Pectoris Cooperative Study, and others suggest that it is not.(161, 159, 137, 163) There is still little indication as to "how good" the prognosis of the asymptomatic patient with significant heart disease really is.

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*Chest pain in such patients is equally as likely to result from cholelithiasis, peptic esophagitis, or ischemic heart disease. The simple demonstration of gallstones, reflux, and/or coronary stenosis by appropriate studies does not permit the physician to establish the proper diagnosis with confidence.

CLINICAL BENEFITS OF ACBG

It is abundantly clear that ACBG is highly successful in abolishing or reducing the frequency and/or intensity of angina pectoris; similar effects have not been demonstrated unequivocably, however, in regard to the other clinical manifestations of the disease. It is possible that benefits other than the relief of pain could exist for certain subsets of patients with the disease and not be apparent in studies of the total population of patients with coronary heart disease. In order to explore this possibility, the cohort of patients with coronary heart disease must be subdivided. The initial, but not necessarily final, classification could be one of two types:

Anatomical: Patients could be classified initially by arteriographic findings, i.e., single vessel, double vesel, triple vessel, left main equivalent, and left main coronary disease. Myocardial contractility also is crucial. As emphasized by Favaloro, the magnitude of the ventricle at jeopardy determines the severity of the disease.(32)

Clinical presentation: Patients could be classified initially by several constellations of presenting symptoms and physical and laboratory findings. Categories could include asymptomatic, angina de novo, chronic stable angina, unstable angina, variant angina, uncomplicated myocardial infarction, acute myocardial infarction and cardiogenic shock, and coronary heart disease associated with valvular heart disease.

An anatomic classification would require that all patients showing clinical evidence of or suspected of having coronary heart disease, undergo coronary arteriography. Such a practice is not without risk, albeit small, and would be economically burdensome to the patient and to society.(174, 175) For the busy practitioner in a society that does not have unlimited resources, the clinical presentation would seem to be the most effective way to classify the patient; it is not thought that great numbers of patients with potentially life-threatening disease, such as critical stenosis of the left main coronary artery, would be overlooked.

It should be emphasized that not all leaders in the field support the use of the clinical presentation for classification of patients with coronary heart disease. Many recommend that coronary arteriography be performed on all patients soon after

suspicion of the disease is raised.(32, 176-178) To implement their recommendations widely, a major expansion of cardiac catheterization and operating facilities and personnel would be required, and it could be accomplished only at great cost to a society already plagued with double-digit inflation. Furthermore, the characteristics and standards of medical practice in this country tend to be adopted elsewhere, so the ultimate results of the decision of how to classify patients with coronary heart disease could indeed be staggering.

In 1977, the Ad Hoc Committee for the Indications for Coronary Arteriography of the Council of Clinical Cardiology of the American Heart Association issued a caveat on this subject.(175) They stated that "there is a growing public concern about the accelerating use of medical technology which is perceived by some to be a substitute for personal medical care, with higher costs and sometimes with less patient satisfaction resulting. If the indications for arteriography are expanded much further, the total national cost will rise even higher than the current, almost intolerable level. Therefore, economic considerations may not be sidestepped."

Nonetheless, consideration of cost should not compromise the quality of patient care. If ACBG is contemplated, the information that can be derived from coronary arteriography is crucial for defining the presence and extent of coronary heart disease. Therefore, arteriography may find its greatest role in evaluating patients with angina pectoris refractory to maximum acceptable medical management. It is essential for all patients who may become part of a research study of the natural history, therapy, or other aspects of coronary heart disease. This is clear. The unresolved and/or debated issue is whether most patients who have coronary heart disease and in whom pain can be controlled should be studied in order to "define" a prognosis for survival. Resolution of this issue will depend on the confidence one has in predicting what the prognosis of a given patient really is at a time when the natural history of coronary heart disease is changing very rapidly and new modes of therapy are being developed, and if the prognosis can be bettered by ACBG.

Relief of Angina

It is generally agreed that for a time following ACBG, symptoms of angina pectoris are initially free of symptoms.(15, 26, 46, 66-69, 110, 137) This widely-held impression is supported by carefully conducted randomized and nonrandomized studies of patients

with stable angina, unstable angina, and left main stem coronary artery disease.(34, 137, 159, 160, 110) The symptomatic improvement is so marked that patients frequently require less medication after surgery than before.(137) Although the placebo effect is difficult to discount completely, most clinicians are persuaded that the relief of pain results from an increase in the perfusion of the ischemic myocardium. However, it should be recalled that 80% of patients improved symptomatically following the Vineberg internal mammary artery implantation procedure, as did over half in whom the internal mammary artery was ligated and 60% of the survivors of the Beck procedure.(179, 180, 9, 181, 182)

Accumulating data suggests that the initial improvement, especially the relief of angina, deteriorates with time after surgery. Attrition rates varying from 5 to 20% per year have been reported.(32, 143, 144, 183-185) One might reason that such deterioration results from the progression of the underlying disease in the native circulation or from changes in the vein grafts. However, it could conceivably be attributable, at least in some patients, to the loss of the placebo effect of surgery. If the graft is patent at one year after surgery, its probability of long-term patency is surprisingly good. As previously discussed, investigators at the Montreal Heart Institute have reported that the annual attrition rate of grafts placed by an experienced surgical team and known to be patent one year after surgery is 0.7%.(119) These investigators have recently extended their observations by analyzing the long-term clinical course of symptoms and function of 75 patients who were able to exercise and had patent grafts one year after surgery.(186) Having carefully conducted studies of these patients, Campeau, et. al. emphasized that the results varied according to the definition of improvement of angina.(186) When improvement, "defined by the New York Heart Association Functional Classification as applied by the Canadian Cardiovascular Society" was considered to consist of betterment by one Functional Class, the improvement rate at seven years was 75.8%. When improvement was defined as disappearance of angina or betterment by at least two to three Functional Classes, 41.9% of the patients had long-term favorable results. Campeau, et. al. found that seven years after surgery the likelihood of attrition of postoperative improvement of angina was not related to the number of involved arteries, the number of grafts, or the degree of revascularization; it appeared to be associated with the progression of atherosclerosis in the native coronary arteries. It was concluded that "the poor long-term results" will persist until effective means of preventing the

progression of the disease in the native circulation have been found and adequately applied," and that "aortocoronary bypass surgery for the treatment of angina is palliative therapy. Until contemporary surgery is shown to be associated with much better results, these observations based on our early experience suggest that aortocoronary bypass surgery for the relief of angina should still be limited to patients who remain incapacitated in spite of optimal medical therapy."(180)

Siedes, et. al. reported similar findings.(143) After excluding patients whose grafts had closed during the first year, they reported that five years after surgery the coronary artery bypass graft in the distal native coronary artery system as a whole appeared anatomically stable. However, the symptomatic status of the patients was not so bright. Eleven of 16 patients who were asymptomatic in the early postoperative period experienced a return of angina pectoris 9 to 67 months after operation; 9 of the 11 had progression of disease in at least one grafted native coronary vessel. In contrast, none of five patients who remained asymptomatic showed such progression of disease in ungrafted native coronary arteries. The authors pointed out that in their small series, operated on during their earlier experience, complete revascularization by present-day standards had not always been attained. They questioned whether the long-term persistence of the relief of angina might have been more common if complete revascularization had been provided. Sheldon, et. al. studying a larger group of less-carefully selected patients during an earlier period after surgery, found that the completeness of revascularization did influence the long-term clinical course.(33)

Based on six years of observation of 19 of 72 patients said to be completely revascularized and studied one year postoperatively, Roberts, et. al. concurred with the previously-cited investigators, who emphasized that progression of disease in the native circulation was the cause of clinical deterioration in most patients.(144) Progression was more common in unbypassed arteries, which were presumably essentially normal before surgery, than in bypassed arteries. They analyzed, however, only lesions that produced greater than or equal to 70% narrowing of the arterial lumen. Observations on their small but carefully studied series raised the interesting possibility that progression of disease in the native, usually ungrafted circulation was the cause of late onset, postoperative angina, which usually was mild and gradual in onset, while graft failure tended to be associated with acute coronary events.

Although clinical deterioration frequently occurs, a large proportion of "deteriorated" patients consider themselves clinically improved over the preoperative state.(191) ACBG remains an effective means of improving, at least for a time, angina that is refractory to more conservative forms of therapy.

Functional Improvement and Work Status

Functional capacity, as measured by treadmill testing, is often improved by ACBG.(33, 101-104, 159, 185) Mathur, et. al. found that exercise time increased whether or not surgery was performed on the patients.(137) The product of heart rate and systolic blood pressure attained with exercise was higher only in those who were operated on, however. Angina could not be provoked during exercise in 22 of 32 survivors who had had ACBG, whereas only 9 of 30 survivors in the medically treated group were able to complete treadmill testing without experiencing angina. More recently, nuclear angiography has demonstrated that ACBG is associated with improved left ventricular function during exercise.(108, 187-190)

Overall statistics suggest that ACBG has less effect on work status than on symptoms, quality of life, and functional capacity.(191-194) A review of the literature does not support Effler's enthusiastic claim that ACBG has returned or will return large number of individuals "from invalidism to gainful employment."(195) In a study of 893 men who had been gainfully employed, Rimm, et. al. found that 11% of those under, and 26% of those over, the age of 55 retired after ACBG.(191) The observed retirement rate was 7.5 times higher than that of the total population for patients in the former and 11.3 times higher for those in the latter age group. Among patients who remained employed, 30% changed occupational status postoperatively, often taking less demanding jobs.

Hammermeister, et. al. compared the work records of medically and surgically treated patients with coronary heart disease one year after cardiac catheterization (used as "time zero" for medically treated patients) or surgery; 74% and 75%, respectively, were working three months before catheterization or surgery.(192) One year after catheterization or surgery 62% of each group was working full-time. These investigators found that the work status three months before catheterization or surgery was the best predictor of employment status 15 months later. Other important

predictors were years of education, age, functional classification before catherization or surgery, and period of unemployment before the event. These investigators concluded that "there is little doubt that coronary surgery can alleviate symptoms and improve exercise performance. We believe that failure to return to work must be largely caused by nonmedical factors. Possible reasons include the patient's fears, economic incentives to remain retired because of pension, disability insurance and Social Security benefits, economic disadvantage to the employer because of workman's compensation insurance; and competition for jobs by younger, healthier people."

Logue, et. al. generally concurred with these conclusions.(193) They observed that patients strongly motivated to return to work because of economic considerations usually did so, whereas those with generous disability programs often retired after surgery. They reported that although 90% of the patients studied at Emory University had symptomatic improvement and relief of angina, only 50% returned to work. These investigators emphasized that the physician may influence the patient not to return to stressful working conditions despite successful surgery. It is sobering to realize that Gross, et. al. found that 56% of 231 patients rejected for ACBG between 1971 and 1974 and treated conservatively returned to work; only nine patients were house-bound.(178) The Cleveland Clinic Group reported that 53, 54, and 53% of the survivors operated on in 1971, 1972, and 1973, respectively, were employed five years postoperatively.(59) The Alabama Group concluded that, contrary to expectations, few rehabilitation benefits appeared to result from ACBG.(194) But some investigators are more optimistic. Lawrie, et. al. stated that the "rate of functional rehabilitation as measured by the number of patients still employed five to eight years after operation remains gratifyingly high at about 85%.(156) Niles, et. al. analyzed a series of 105 patients who underwent ACBG.(196) They found that after surgery, 92% of the patients experienced relief or improvement in angina and there was a 10% net increase to the work force; at the time of operation, 50% of the cohort had worked within one month, 31% had not done so and were either unemployed or on sick leave, and 19% were retired.

Even more impressive was a report from the Hammersmith Hospital in London.(195) Of a group of 130 patients operated on in 1976-77, only nine out of 117 men were working full-time without restriction or were doing light work before surgery whereas afterwards 70 were working without restriction or engaged in lighter work. (P less than 0.001) The investigators concluded that the differences were most pronounced among

heavy manual workers, of whom none could work normally before surgery, but 16 of whom were working without restriction afterwards. Anderson, et. al. studied 564 male patients one and four years after ACBG and found that for age categories of less than 55, 55 to 59, and at least 59 years at the time of operation, 90%, 68%, and 44%, respectively, remained employed four years later.(198) Furthermore, of patients not employed prior to surgery, 22% were employed four years later.

The social acceptability of earlier retirement, managerial considerations, and variability among physicians' standards may obscure the accomplishments of both medical and surgical treatment in rehabilitating patients with coronary heart disease. Clearly, rehabilitation for gainful employment following ACBG would appear to be an area of fruitful endeavor in the future.

Control of Arrhythmia and Prevention of Sudden Cardiac Death

The frequency and complexity of ventricular arrhythmias have been related to the extent of coronary obstruction and myocardial fibrosis, and the severity of ischemia both at rest and as a result of stress. There is increasing evidence that ventricular arrhythmias may herald sudden death. Therefore, it is not surprising that ACBG has been undertaken in selected patients to control and/or prevent these complications.

Despite initial enthusiasm for the use of ACBG in treating recurrent arrhythmias, most investigators now consider that the procedure is of limited value for this purpose.(100, 199-210) Lown and Graboys, reviewing the treatment of malignant ventricular arrhythmias, concluded that "preliminary data suggest that the coronary bypass procedure has little if any salutary action on ventricular arrhythmias."(206) Mullins, et. al. in a critique of ACBG, likewise concluded that "more extensive experience with larger numbers of patients with medically refractory ventricular tachycardia due to coronary artery disease has led to some skepticism as to the usefulness of surgery. The arrhythmia in several reported patients persisted after coronary bypass surgery. This suggests that the operative procedures are indicated after all medical therapy, including pacemaker suppression, has been exhausted."(100)

In their randomized study of 116 patients with stable angina, Guinn and Mathur did not find a difference in the incidence of arrhythmias.(111) Furthermore, continuous

electrocardiographic monitoring during ordinary activity showed no difference in the incidence of ventricular arrhythmia between the medically and surgically treated groups in the Randomized VA Cooperative Study of Stable Angina.(34)

Tilkian, et. al. analyzed the prevalence of arrhythmias in 84 patients followed for one year.(207) Forty-two of the patients were randomized to surgery and 42 to medicine, and the incidence of ventricular arrhythmias appearing during treadmill testing was determined at the beginning of the study and one year later. Significant changes in frequency or severity of exercise-induced ventricular arrhythmias were not observed following ACBG. Higher-grade ventricular arrhythmias occasionally occurred after successful ACBG, however. Patients with all grafts patent had the greatest improvement in exercise capacity and achieved higher heart rates with less evidence of myocardial ischemia; however, this subgroup showed a tendency to more frequent and higher grades of arrhythmias.

Occasional reports of recurrent arrhythmias' responding to or "being controlled" by ACBG in conjunction with resection of discrete ventricular aneurysms have been published.(204, 208) These reports have not been adequately controlled and usually have discussed a small number of patients followed for a short period of time. Ricks, et. al. reviewed the experience of 21 patients with refractory arrhythmias who received ACBG at Stanford.(208) Three of these patients had severe hypokinesis and 18 had ventricular aneurysms documented angiographically prior to surgery. These investigators concluded that surgery performed during the relatively unstable postmyocardial infarction period was associated with an 80% mortality rate; one month or more after infarction this rate was 20%. After an average of 36.5 months, 13 of 21 patients were alive despite persistence of ventricular arrhythmias.

Recent reports of guiding the resection of the site of origin of recurrent ventricular tachycardia by both endocardial and epicardial mapping during induced ventricular tachycardia are encouraging. Horowitz, et. al. at Philadelphia have reported complete resection of the site from which the arrhythmia arose in 27 of 30 patients and partial resection in the remaining three.(211) Aneurysmectomy was performed in 27 and ACBG in 21. Two operative deaths and three late nonarrhythmically-related deaths occurred. One of the 25 surviving patients had had ventricular tachycardia during the 4- to 28-month follow-up.

At least two groups have reported encouraging results regarding the role of ACBG in reducing the incidence of sudden death. Hammermeister, et. al. retrospectively analyzed the three-to-five-year course of 1,180 surgically and 350 medically treated patients followed by the Seattle Heart Watch Vismara, et. al. reported follow-up of 264 patients with two or three-vessel disease studied between 1970 and 1973.(212, 213) Both groups of investigators suggested that the incidence of sudden death was reduced in operated patients. A number of questions have been raised, however, about the appropriateness of the control populations. The results of these two studies, although not conclusive, should not be discounted, for if ACBG were confirmed to postpone the occurrence of sudden death, more general use of ACBG might be indicated. Because prevention of sudden death would allow the at-risk patient to seek hospitalization, delayed death might also be prevented. To demonstrate conclusively that one benefit of ACBG is preventing sudden death, a study will have to be carefully designed and executed. Based on current knowledge, prevention of "sudden death" would seem to imply postponement of "slow death."

The preponderance of currently-available data concurs with Frick et. al. who, after reviewing available data, concluded that, except in patients having left main stem coronary artery disease and depressed left ventricular function, "in general, data analyzed do not strongly favor surgical therapy as a means of reducing the rate of sudden death, or death in general for that matter. It is worth emphasizing, however, that in no report has surgical treatment been inferior to medical management . . . the exact value and role of coronary bypass surgery in the treatment of coronary heart disease still remains to be solved."(214)

Prevention or Control of Congestive Heart Failure

Morris, et. al. were among the first not to reject a patient with angina pectoris from consideration for ACBG because of the presence of congestive heart failure.(215) In 1970, they reported a total hospital mortality of 8.7% in 161 patients, 48.2% of whom had elevated LV end-diastolic pressure. The pressure was 20 mm/Hg in 13.5% and 25% had symptoms of congestive heart failure. Among the patients with congestive heart failure prior to ACBG, 82% were said to have improved postoperatively, 9% to have been unchanged, and 9% to have been worse at an unstated follow-up period. Mundth, et. al. reported a similar experience.(216) They operated on 40 patients with ischemic

heart disease and severe congestive heart failure and followed them for up to three years. Preoperatively, 26 had significant angina pectoris and 11 had a ventricular aneurysm. Of the 31 survivors, 80% had good to excellent clinical results.

The presence of significant angina pectoris in patients with severe congestive heart failure, according to Spencer, et. al. at New York University, improved the prognosis following ACBG.(217) Cardiac catheterization 6 to 10 months after surgery in 10 patients who had congestive heart failure without significant angina demonstrated no improvement in myocardial contractility or reduction of elevated LV pressure. Based on these observations, it was concluded in 1971 that advanced congestive heart failure secondary to diffuse hypokinesis but without angina probably should be considered inoperable. Others active in the field generally share a similar opinion.(218-220)

A number of investigators have recently stated that such patients can benefit from ACBG and should not be denied the opportunity.(47-50, 221, 222) Kay and his associates have supported such a philosophy for many years.(47, 49) In 1977, they reported only 31 hospital deaths in 140 patients with ejection fractions of 0.2 or less. An actuarial curve revealed that at six years, 59% of the surgically treated patients were alive, as opposed to only 22% of a medically treated group. The controls consisted of 79 patients who were offered surgery (between February, 1969, and January, 1976) but who declined it.

With further experience and improved surgical techniques, the group at New York University reversed their earlier pessimistic opinion regarding surgery for patients with significant impairment of LV function.(48, 217) Isom, et. al. stated that "consideration of the problem focuses on the important question of whether coronary artery bypass preserves left ventricular muscle by protecting from further infarctions. If it does preserve muscle, the patients with impaired left ventricular function actually need coronary bypass more urgently than those with normal left ventricular function since further reduction from an additional infarction may either be fatal or precipitate intractable congestive failure."(48) They reported an operative mortality of 9.7% in 62 consecutive patients operated on between January, 1971, and May, 1974; these patients all had severe angina, a hypokinetic left ventricle, and an LV end-diastolic pressure greater than or equal to 20 mm/Hg. The life-table analysis showed a two-year survival rate of 85%. The team concluded that, "with current

techniques impaired ventricular function is not a major contraindication to bypass grafting." Johnson and his colleagues at Milwaukee recently reported that following ACBG, 16 of 19 patients with ejection fractions less than 40% (mean 31%) demonstrated with exercise a response toward normal with a maintenance or increase in the ejection fraction and no deterioration of regional wall motion. (223)

Many of the patients included in these more recent reports received not only ACBG with attempts at total revascularization, but also procedures such as LV plication, aneurysmectomy, and mitral valve replacement. On the other hand, many of the patients in the control population had not been given the most advanced noninvasive therapy.

It is possible that patients with congestive heart failure, especially those with significant angina, may enjoy a more comfortable, productive, and possibly even a longer life than medically-treated patients, provided they have the advantage of competent surgery. Clearly, radionuclide techniques will be useful in identifying patients with significant ischemia but viable myocardium. Whether all patients with intractable congestive heart failure, a select subset, or an occasional patient, will enjoy such results is unknown. However, it is unlikely that the lowering of mortality reported for these critically ill patients can be duplicated throughout the country; the several groups reporting these improved statistics have each emphasized the importance of meticulous attention to technical details designed to preserve the myocardium.

There are no data to indicate that ACBG is useful in preventing the development of congestive heart failure. It has been suggested that patients with perioperative myocardial infarction are quite likely to develop congestive failure and that graft occlusion may predispose a patient to the development of congestive heart failure.(73, 74, 84) It might be reasoned that if ventricular contractility improved after ACBG, congestive heart failure might be less likely to occur.(108) Such improved contractility probably occurs in at least one-quarter of patients.(109) Furthermore, if ACBG prevents the occurrence of myocardial infarctions, as discussed in the following section, congestive heart failure might be prevented.

Prevention of Myocardial Infarction

An acute myocardial infarction is, next to death, the most serious clinical manifestation of coronary heart disease. The Framingham data, collected for 20 years beginning in 1948, indicated that one in five men who had a first myocardial infarction died within one year; such men had a mortality rate 14 times that of those free from coronary heart disease.(224) In men who survived the first year after a recognized myocardial infarction, the risk of dying was increased by 23% for the following five years, or four times more than the general population, and 25% for the five years thereafter or more than three times the general population. The prognosis was distinctly worse in women than in men because of a higher early mortality rate (45%). Patients with both recognized and unrecognized myocardial infarctions had similar survival rates after three years. Within the first five years, a second myocardial infarction occurred in 13% of the men and 40% of the women. Harris, et. al., after analyzing the courses of 1,214 patients treated medically and followed for seven years, emphasized that a nonfatal infarction might drastically alter a patient's prognosis; among patients with normal left ventricular function, a continuing relatively high rate of nonfatal infarctions was likely to maintain or even increase the mortality rate over a long follow-up period.(225) Thus, improving the long-term survival rate in patients with multivessel disease and good ventricular function may depend on decreasing the incidence of nonfatal ischemia events, which consist mainly of acute myocardial infarctions.

Whether the occurrence of myocardial infarction has declined with the death rate for coronary heart disease in this country has not been clearly established. Suggestive evidence was reported from the Kaiser-Permanete Medical Care Program of Northern California, where investigators found that the proportion of persons hospitalized each year for acute myocardial infarction dropped 27% in a fairly steady fashion, from 4.5 per 1,000 policy holders in 1971 to 2.96 per 1,000 in 1977.(226) The improvement was apparent in both sexes and all age groups. Based on the results of this study, it would appear that both new and recurrent infarctions have decreased in incidence. If the occurrence of both new and recurrent myocardial infarctions is declining, the use of data collected in an earlier era as a control is fraught with uncertainties and potential biases. In addition, the ability to diagnose an acute myocardial infarction has greatly improved during the last decade. Therefore, to determine the role of ACBG in preventing acute myocardial infarctions, studies mut be randomized or have concurrently managed controls.

The major end-point of the randomized studies of ACBG has been death, but most investigators also reported the occurrence of myocardial infarction. There is no evidence that ACBG reduced the incidence of myocardial infarction in the randomized studies of stable angina pectoris by Mathur and Guinn, Kloster, et. al., the New Zealand study, and the European Multicenter Randomized Aorto-Coronary Bypass Study.(111, 137, 159, 161, 227) Although the randomized VA Cooperative Study of Chronic Stable Angina has not published data on the subject, it acknowledged reports that there was no difference in the incidence of myocardial infarction between the medical and surgical groups.(34) Similarly, the randomized NHLBI Study of Unstable Angina Pectoris provided no evidence that ACBG prevented myocardial infarctions.(160) However, the large number of crossover patients weakens confidence in this statement.(110) Finally, even in the randomized study of left main coronary artery stenosis, at 30 months, 10 myocardial infarctions each were recorded as having occurred in the medical and the surgical groups.

It should be noted that in each of the randomized studies, perioperative myocardial infarctions were included in the total number of infarcts. As has been indicated, the incidence of such events is declining in most centers. It is possible that data may be forthcoming to indicate that ACBG will reduce the incidence of acute myocardial infarction.

The Role of ACBG in the Asymptomatic Patient

The dilemma regarding the use of ACBG in the management of asymptomatic patients has not kept many centers from recommending the procedure.(32, 229-235) Such treatment is frequently justified by statements such as "the patients really were not asymptomatic; if they were, they would not have been studied initially." Unfortunately, as previously stated, more than a few such patients have been identified as a result of the patient or physician requesting a stress test before initiation of an exercise program of some sort. It is occasionally said that supposedly asymptomatic patients have modified their lifestyle so as to avoid symptoms. In some centers, patients who have recovered from a myocardial infarction and currently have no symptoms are classified as asymptomatic; used in this paper, however, such patients are included with others who have had a myocardial infarction.

In an effort to develop a strategy for managing the asymptomatic or mildly symptomatic patient, Grondin, et. al. reported a four- to eight-year follow-up of 55 patients who underwent prophylactic coronary artery grafting.(230) Sixteen patients had no angina and 39 could be categorized in the New York Heart Association's Functional Class I. Twenty-one patients had single-, 13 double-, and 27 triple-vessel disease. The group received a total of 101 grafts. No deaths occurred, but two patients suffered perioperative myocardial infarctions and three required further surgery for persistent bleeding. Nine of 45 grafts studied early after surgery were occluded; two patients had occlusion of all grafts at one year, and one had such a finding at five years. Of the four late deaths, three were related to coronary artery disease. Only 31 of 51 survivors (60.8%), examined a mean of 69.3 months after surgery, were free of angina. These investigators concluded that, based on their retrospective study, such asymptomatic patients stood to benefit little from prophylactic revascularization.

The central issue, previously alluded to, is that although coronary arteriography is a reliable indicator of the anatomic presence of coronary artery disease, just as an oral cholecystogram is a reliable indicator of cholelithiasis, neither the arteriogram nor the cholecystogram necessarily identifies those patients in whom the disease is physiologically significant. Coronary artery disease and ischemic heart disease appear to differ in prognosis. It is well known that the diagnosis of angina pectoris is fraught with both many false positive and many false negative conclusions, but angina and other clinical symptoms remain the keystone in determining when coronary artery disease becomes ischemic heart disease. Harris, et. al. found progressive chest pain and nocturnal angina to be two of seven non-invasive, highly discriminating, independent predictors of prognosis.(236) Although far from precise, clinical manifestations give some insight into the tempo of ischemic heart disease; they represent in part the "malignancy factor" of the process.

Sometime in the future, the natural history of asymptomatic coronary artery disease, diagnosed on the basis of anatomical findings, may be defined. A number of centers now are presenting preliminary anatomical data on relatively small series of asymptomatic patients. For example, Hickman, et. al. reported studies of 90 males 45 $\pm$ 4.7 years old who were followed 57 $\pm$ 2.5 months.(237) Seventy-eight of the patients had lesions producing greater than 50% stenosis, and 12 had lesions producing between 30% and 50% stenosis. Seven of the patients received surgery, four while still asymptomatic. Of the remaining 83 patients, 16 developed symptoms after an average

follow-up of 31 ± 5 months, 16 developed angina, 4 sustained a myocardial infarction, and 2 died suddenly. The authors concluded that the five-year prognosis for such patients is good, even for high-risk patients; that the angiographic severity is not a strong predictor of coronary events, whereas evidence exists that the presence of three or four risk factors may be; and that angina, as opposed to sudden death or myocardial infarction, is the most common initial coronary event in such patients.

Until the results of further studies are available, decisions regarding the use of surgical therapy ought to be based on the symptomatic or physiologic manifestations of ischemic heart disease. At present, this is most frequently accomplished largely by eliciting clinical manifestations. Even the predictive value of the exercise stress test diminishes if asymptomatic patients, without a history of previous cardiac events, are examined; both the specificity and the reliability of such tests are markedly decreased in this population.(238, 239) Radionuclide perfusion scanning and radionuclide angiography, particularly if performed during both rest and exercise, two dimensional echocardiography during rest and stress, and stress ventriculography coupled with coronary arteriography show promise as indicators of severity of ischemic heart disease, but their prognostic value is yet to be defined.

It must be remembered that coronary artery disease is not a relentlessly progressive process.(172, 240) Postoperative angiographic studies designed to define graft patency and rates of progression of disease in the native circulation have confirmed this impression. As previously noted, Bourassa, et. al. reported that only 3 of 13 grade 1 or 2 lesions in the left main coronary artery progressed to grade 3 stenotic lesions over a six-year period.(139) Furthermore, myocardial infarction and sudden death, the two disasters against which prophylactic operations are aimed, are not necessarily caused by progression of a critical lesion.(172) Other mechanisms include thrombosis in situ, embolization, rupture of an atherosclerotic plaque, and subintimal hemorrhage. None of these mechanisms is limited to severely obstructed coronary arteries; each may occur at sites of leser lesions which may not be receptive to bypass grafts, either.

Furthermore, there is no clear-cut evidence that ACBG prevents the occurrence of a myocardial infarction or sudden death; its greatest proven usefulness is in treating the pain of angina pectoris. As has been emphasized, this relief is not always

longstanding; and as will be discussed subsequently, second operations carry increased risk and a decreased incidence of clinical improvement. The asymptomatic patient, of course, cannot appreciate a symptomatic benefit from the operation. It would appear likely that proper timing exists for the execution of an ACBG, if this procedure indeed is indicated. In managing the asymptomatic patient, the clinician must truly ask the surgeon: "you can . . . but should you?"(3)

The Role of ACBG in Angina de Novo

The appearance and recognition of angina de novo change coronary heart disease to ischemic heart disease. Some clinicians view the mere appearance of angina de novo as equivalent to unstable angina. Others recognize that such angina is often transient or responsive to medical management and consider arteriography and ACBG only when symptoms prove consistently incapacitating. Others follow a middle ground.

Older studies of natural history are of limited use in discussing the role of ACBG, as coronary arteriography was not performed.(241, 242) Nevertheless, during follow-up periods of from four-and-a-half to 14 years, men who presented with angina were reported to experience the risk of myocardial infarction and death two to three times more than men of comparable age who were initially free of the manifestations of coronary artery disease. More recently, Duncan, et. al. observed the clinical course of 129 medically treated patients in whom angina had developed for the first time within the preceding four months.(243) Fourteen percent went on to suffer myocardial infarction or to die suddenly; most of these events occurred within six weeks of the onset of angina. The effect of such measures as the prompt administration of beta blockers and the cessation of smoking on the incidence of these complications is unknown. These investigators, however, concluded that angina, "even when severe and of recent onset is transient in many patients;" they stated that the syndrome of new angina "has a low risk of serious cardiac complications."

There is clearly no uniform opinion as to how the patient with recent onset of angina should be managed and whether coronary arteriography is indicated as soon as the diagnosis is established. Some might take the attitude that every such patient has potentially significant left main coronary artery stenosis and feel compelled to contemplate surgery. But it would appear that even this anatomic presentation

represents a spectrum of severity, and urgency is not always indicated.(244) Whether arteriography is performed will depend on whether the clinician's attitude towards decisions regarding surgery are determined more by cliical and physiological manifestations, or by anatomical findings. Regardless of the reasoning, if every patient with new-onset angina were studied angiographically, the health care delivery system would become a victim of an enormous economic burden. If ACBG definitely and consistently would postpone death and prevent myocardial infarction, such an expenditure would be justified. Until such information is available, however, a prudent course is recommended.

The Role of ACBG in Chronic Stable Angina

A review of the literature shows that the role of ACBG in the management of chronic stable angina is one of the most hotly debated areas in modern medicine.(35-39, 153, 162-168) At least 300,000 patients in the United States received an ACBG through 1977.(15) Based on a conservative estimate, an additional 200,000 patients have probably received an ACBG from 1977 through 1979 in this country. Yet only about 900 patients with stable angina were studied, randomized to operated and nonoperated groups, and followed for periods approaching three years in order to define the benefits of the procedure.(34, 110, 111, 159) Except for patients with disease of the left main coronary artery and possibly those with severe three-vessel disease and a decreased ejection fraction, there is no conclusive evidence that surgery prolongs life more than medical therapy does.(110) The reliability of the data, as well as the conclusions drawn regarding the benefits of surgery, have been repeatedly challenged and discussed. Suffice it to say that in the judgment of this author, additional large randomized studies to evaluate the role of surgery in prolonging life still are needed.(245) Others support this opinion. Angell, responding to a presentation by Loop entitled "A Surgeon's View of Randomized Prospective Trials," stated that "I personally must still believe that randomized prospective studies have a place despite the problems. We physicians need the conviction of real data that will stand criticism of our colleagues, for it will force us to resist the pressures of busy practices, active lives, and economic burdens, and will guide us to do what is right for the patient rather than to feel or to rationalize what is right."(166, 165) But despite such desires, Hurst, et. al. are probably correct in their opinion that "it is unlikely that new prospective randomized studies comparing the effect of bypass surgery with medical therapy will

be initiated. The problems created by the studies in progress have blunted the enthusiasm of [sic] such an approach."(26)

Two randomized studies of stable angina underway outside this country should be cited. In March, 1978, Favaloro reported the preliminary results of a prospective randomized study of stable angina being conducted in Argentina.(32) After a 34-month follow-up of 53 operated and 50 nonoperated patients, the mortality rates were 5.6% and 2%, respectively. The second study is being conducted by the European Coronary Study Group.(227, 228) Three hundred seventy-three patients were allocated to medicine and 395 to surgery; as of the most recent report, they have been followed for three to five years. All patients were males under 65 years of age with mild to moderate angina pectoris, at least two-vessel disease, and good left ventricular function. "The policy of surgery was associated with significantly better tive year survival than that of no surgery; the rates were 93.5% and 84.1% respectively." The figures for patients with left main disease were 92.9% and 61.7%, and 94.9% and 84.8% respectively for those with three-vessel disease. The authors point out that the report should be considered as interim and the results preliminary, as the total follow-up for all patients is expected to be five years. This interim report implies that outcome does not differ significantly between medically- and surgically-managed patients with two-vessel disease; contributing factors appear to include a high survival rate for the medical patients and appreciable preoperative and perioperative mortality among surgical patients. The continued follow-up of these patients is clearly important. This study is not susceptible to many of the criticisms leveled at the VA Cooperative Study.(34) Operative in-house mortality was 3.6% in all operated patients and 1.5% in the last third. An average of 1.9 grafts per patient were inserted in the two-vessel disease subgroup and 2.4 grafts per patient in the three-vessel subgroup. Graft patency was 90% after 9 months and 77% between 9 and 18 months.(227)

The results of both of these studies, conducted outside this country, must be applied with caution to decision-making in patient care in the United States.(32, 227) What is the natural history of coronary heart disease in the societies from which the study cohorts are derived? Is mortality declining, as in this country, or continuing to rise, as in much of the world? The Pan American Health Organization cannot supply data regarding Argentina, but mortality is continuing to rise in neighboring countries. The European study embraces some societies in which mortality from coronary heart

disease is continuing to rise and others in which it is declining. It would seem reasonable that a specific form of therapy might be quite beneficial in a society where the natural history of the disease is characterized by a progressive rise in the annual mortality. Yet the same therapy might be of little benefit if the mortality is declining, as it is in this country.

Regardless of the above reservations, the results of the European Study show decisive differences following surgery for patients with left main and possibly three-vessel disease.

Because of the difficulty of conducting randomized studies, a computer program was developed at Duke Medical Center which permitted the collection of large amounts of data on consecutively evaluated patients. A two-year follow-up was published in 1974 and included 379 patients who had undergone ACBG and 402 who had concurrently received medical treatment.(155) The two groups were found to differ in only a few of the 89 clinical parameters monitored; the survival rate was essentially the same in both groups (85% surgical, 83% medical). A subsequent report with more patients and a four-year follow-up showed an 83% survival rate among 490 surgically treated patients and a 75% survival rate among 611 medically treated patients.(154) Although the difference was not statistically significant for the groups as a whole, certain high-risk categories in which ACBG appeared to offer an advantage were identified. Specifically, patients with the combination of total occlusion of the right coronary artery and subtotal occlusion of the left anterior descending artery showed a three year survival rate of 88% after ACBG, compared with only 68% (P less than 0.01) for the medically treated controls.(154)

Hammermeister, et. al. also reported an advantage for surgical management of patients with two coronary arteries affected by stenosis greater than or equal to 70%.(246) When 97 such patients were matched with medically treated patients according to several independent variables predictive of survival, five-year survival was found to be 95% in the former but 76% in the latter ($P = 0.0002$).

Patients with single-vessel coronary heart disease have such a low annual mortality (2% or less) that surgical intervention to promote survival has not been encouraged generally.(15, 27, 103, 165) The outlook is less favorable for isolated disease of the

proximal segment of the left anterior descending artery (3 to 4% annual mortality), but was not clearly improved by ACBG.(247) Kouchoukos, et. al. reported a retrospective analysis of 53 patients with high-grade occlusive disease confined to the proximal left anterior descending coronary artery, stable angina, and no significant impairment of left ventricular function.(248) In 29 surgically treated patients with a mean follow-up of 24 months, there were no postoperative deaths, two late deaths (7%), and five myocardial infarctions (4%). Surgical treatment was more effective in relieving angina and improving exercise tolerance performance, but showed no advantage in terms of survival or incidence of myocardial infarction.

Although the anatomical extent of coronary heart disease is an important predictor of survival in groups of patients, its prognostic value in the individual patient is limited. Thus, other predictors have been sought. Vliestra, et. al. report that the most reliable predictor of two-year survival for both medical and surgical patients with coronary heart disease was the LV ejection fraction.(249) One hundred thirty medically treated patients who were acceptable for surgery were compared with 284 surgically treated patients. The four-year survival was equally high in both the medical and surgical groups when the ejection fraction was greater than or equal to 0.50; the two-year survival was low in both groups when it was less than of equal to 0.25. Only in patients with intermediate ejection fractions was there a significant difference between surgical and medical management, with three-year survivals of 89% and 68%, respectively (P less than 0.05).

Lawrie, et. al. used another approach to find a "denominator" for the "numerator" of patients receiving ACBG.(156) These investigators compared longevity after ACBG in a heterogenous group of 434 patients followed for more than five years to the anticipated survival of "the population-at-large without heart disease." This group did not include only patients with stable angina; the problems inherent in using such a control have already been discussed. Nevertheless, the investigators reported that, "the average crude annual attrition rate after the first year was 2.3%, which approximates that of the general U.S. population after correction for age and sex." By excluding the first year, the unacceptably high (by current standards) operative mortality rate of 7.1% could be discounted in evaluating survival. The investigators point out that "in the next 677 consecutive patients the survival after five years was 91.4% (including 4.7% operative mortality rate) compared with the survival of a smiliar normal population of 92.7%." The current operative mortality reported by this surgical group is less than 2%.

Mathur, et. al. recognized the difficulties in defining controls and "selected for further analysis subsets of patients whose poor prognosis has been demonstrated consistently and without doubt."(250) They found that 304 such patients with three-vessel disease had an overall five-year survival of 93.4% following surgery. This survival, they pointed out, is so close to the expected survival of the "normal" U.S. population "that it is unlikely that such results after surgery are due to chance."

Numerous other studies could be cited, but they would contribute little to understanding the role of ACBG in treating stable angina. The recurring point is that longevity of patients with stable angina who receive ACBG is good, but so is that of the medically treated patients. It would appear that surgery, however, does postpone death in patients with left main and possibly triple vessel disease more than can be expected from medical therapy alone.

The Role of ACBG in Unstable Angina

Unstable angina is the clinical condition in which ACBG might be expected to show, most clearly and most quickly, an advantage over medical therapy. Randomized and controlled studies, however, have failed to establish significant differences in prevention of myocardial infarction or prolongation of survival in those patients. In a National Cooperative Study, 288 patients with unstable angina were assigned randomly, after establishing feasibility by arteriography, to either medical or surgical therapy.(160, 251, 252) After a mean of 24 months of follow-up after hospital discharge, it was concluded that in-hospital mortality was low and comparable for the two groups (medical 4.1%, surgical 5.0%) as was late mortality (medical 5.0%, surgical 5.2%). The incidence of early myocardial infarction was higher in the surgically-treated group (18%) than in the medically treated group (10%); the rate of late infarction, however, was 13% in both groups.

A review of the literature in 1976 disclosed 743 published cases of unstable angina in which the patients were treated surgically; the hospital mortality rate was 8.4% and the incidence of myocardial infarction was 8.7%.(253) Among 506 patients with unstable angina treated medically, there was a 5% hospital mortality rate and a 4% incidence of myocardial infarction. In the first 350 patients undergoing ACBG at Stanford, 55 were classified as having unstable angina and their operative mortality

was 11.0%, in contrast to 1.4% in patients with stable angina.(184) Other groups also reported higher complication rates in early surgical experiences in patients with unstable angina. It is now accepted that the patients should be stablized with propranolol and vasodilators and, if necessary, intra-aortic balloon counterpulsation prior to study and possible surgery. Ahmed, et. al. recently emphasized again the high prevalence of left main stenosis or severe disease in the anterior descending artery proximal to the first septal branch.(255) Seventy of 71 patients studied and operated on as emergencies between June, 1973, and June, 1978, had such a lesion.

The Role of ACBG in Variant (Prinzmental's) Angina

The current decade will see increasing attention directed to studying the so-called variant angina of Prinzmental. The importance of this clinical presentation became apparent as the last decade closed. In 1974, a review of 90 cases in the literature disclosed a 39% incidence of sudden death or acute myocardial infarction, often within months of the onset of symptoms.(256) More recently, coronary arteriographic studies have allowed the delineation of two separate forms of variant angina. One group of patients has normal or near-normal coronary arteriograms and a long history of nonexertional angina, no previous infarction, and a generally benign course; the other has obstructive coronary lesions associated with unstable angina of recent onset preceded by effort angina and with a high incidence of myocardial infarction and life-threatening arrhythmias.(257)

Great strides have been made during recent years in understanding the mechanism whereby ischemia in this presentation is produced.(258-261, 24) Furthermore, the process can now be studied in the laboratory, almost at will, by administering ergonovine maleate intravenously.(259) The role of the family of calcium-inhibiting drugs in the phenomenon of coronary spasm is currently being explored in many laboratories, and the incidence of spasm superimposed on fixed obstructive lesions is attracting special attention.(24, 262)

The role of ACBG in treating patients with variant angina is currently more confused than that with regard to most other clinical presentations of coronary heart disease. Initial reports by MacAlpin and Gaasch, et. al. were not encouraging.(263, 264) A more favorable experience was reported from The Massachusetts General Hospital: 27

patients with variant angina and fixed coronary occlusive lesions affecting at least 70% of the lumen in one or more coronary arteries have undergone ACBG.(265) Equal proportions of these patients received a single bypass, two bypasses, and three bypasses; two operative deaths occurred. Among the 25 survivors, 63% were reported to be free of pain for up to two years; the other patients were reported to have angina but to be functioning reasonably well.

This group has recently updated its experience with this clinical presentation by describing 54 patients.(266) Nine patients with greater than or equal to 50% but less than or equal to 90% fixed obstruction and 26 patients with greater than or equal to 90% fixed obstruction were operated on. The operative mortality for these 35 patients was 2.9%. Fifty-five percent of the former and 73% of the latter group "experienced marked improvement in their angina states." There was one late death 32 months after surgery and one month after the reappearance of exertional angina. Among the patients without hemodynamically significant obstruction who were operated on, there was one perioperative death and one late death at 18 months as a result of a cardiovascular accident only one patient had relief of angina.

The role of ACBG in this clinical presentation remains to be seen, but studies of the syndrome afford an opportunity to overcome much of our present ignorance about coronary heart disease. The role of ACBG will depend on the effectiveness of drugs such as nifedipine, which inhibits calcium flux. In introducing a recent symposium on the subject, Lown stated that the interest in the study indicated that "cardiologists are growing resistive at being only technicians in referring patients to the surgical conveyor belt for a costly, but largely palliative solution to the problem of ischemic heart disease."(24)

The Role of ACBG in Uncomplicated Myocardial Infarction

Patients who recover from a myocardial infarction, whether clinically recognized or "silent," are known to have a reduced life expectancy.(267-272) Medalie and Goldbourt followed 9,509 healthy adult subjects over a course of five years; they found an average annual incidence of 5.3 clinically recognized and 3.6 unrecognized infarcts per 1,000 persons.(267) A seven year follow-up showed a higher mortality rate among subjects with evidence of an unrecognized infarct (17.3 per 1,000) than among those with no evidence of an infarct (4.6 per 1,000), but mortality was significantly lower than that observed in those in whom a clinical infarct developed (36.3 per 1,000). Some

investigators propose that underlying multivessel disease should be sought and surgery performed in patients who recover from inferior myocardial infarction, even in the absence of serious clinical symptoms.(272) But convincing data are not yet available that show whether an ACBG performed after a patient's recovery from transmural myocardial infarction, either silent or clinically apparent, will prevent subsequent myocardial infarction or postpone death. As noted earlier, Barrett-Boyes recently reported preliminary data from a randomized study of male patients, most of whom had triple vessel disease. All subjects had suffered two or more documented myocardial infarctions, remained asymptomatic, and were considered good-risk candidates.(161) The study, which is continuing, has shown no advantage with regard to either survival or subsequent myocardial infarction following surgical treatment.

On the other hand, Rogers, et. al. retrospectively evaluated 129 patients who underwent diagnostic and left ventricular angiography within 60 days after an acute myocardial infarction.(273) Ninety-four of the 124 patients had a left ventricular ejection fraction greater than 25% and two or more residual jeopardized ventriculographic segments. Forty-three had ACBG; 51 did not. At a mean follow-up of 23 $\pm$ 2 months after the myocardial infarction, the cardiac mortality was 7% (3 of 43) in the surgical group and 16% (8 of 51) in the medically managed group. This difference is not significant, however, the frequency of sudden death during the follow-up period was 0% in the surgical and 12% (6 of 51) in the medical group (P less than 0.05).

The recognition of possibly serious prognostic implications of nontransmural myocardial infarctions leads to the consideration of such an event's being essentially an "incomplete" myocardial infarction.(268-275) Cannom, et. al. compared the clinical courses of 188 consecutive patients admitted to the hospital with a history of chest pain and elevated enzyme levels consistent with acute myocardial infarction according to whether evidence of transmural damage was present.(269) Patients defined as having subendocardial infarction experienced higher rates of sudden death (33% versus 15%), higher rates of death from all cardiac causes (42% versus 24%), increased incidence of angina (61% versus 36%), and a higher incidence of subsequent myocardial infarction (26% versus 12%).

Schroeder, et. al. reported a retrospective study of 170 patients who were admitted to a coronary care unit because of prolonged ischemic chest pain and transient ST

segment changes, and who lacked confirmatory evidence of myocardial infarction during their hospital stays.(274) During a mean follow-up period of 17.9 months, mortality rates from cardiovascular causes were 4.1% at one month, 10.1% at one year, and 19.7% for the entire follow-up period. Ten of 23 deaths (40%) were sudden; the remainder resulted from acute myocardial infarction or its complications. Another 21 patients experienced nonfatal myocardial infarctions during the follow-up period. The data were interpreted to indicate that patients with suspected myocardial infarctions that did not evolve in the coronary care unit were at high risk for serious cardiovascular events after hospital discharge.

Madigan, et. al. were interested in determining whether the poor prognosis of patients having subendocardial infarction could be altered favorably by surgery.(270) They prospectively studied 50 consecutive patients who survived a nontransmural myocardial infarct. Occlusive lesions greater than 75% in at least one vessel were present in all 50 patients; 30 patients had either double or triple vesel disease. During a mean follow-up of 10.6 months, only 24% of these patients remained free of angina, whereas 30% suffered from stable and 46% from unstable angina. Twenty-eight patients underwent ACBG within three months after their subendocardial infarcts.(275) All but one had continued to experience angina while in the hospital, and all but four were having pain at rest. One patient died immediately after surgery, and the electrocardiograms of three others demonstrated new Q waves. During a mean follow-up period of 16 months after ACBG, 22 patients had no angina and there were no late transmural myocardial infarcts or late deaths.

Acute Myocardial Infarction and Cardiogenic Shock

Clinical experience has generally dictated the avoidance of surgery in patients with acute myocardial necrosis. Experimental data indicate that increasing blood flow after temporary coronary occlusion is not beneficial and that, in fact, it may lead to myocardial hemorrhage and extension of the infarcted area.(25, 276) Nevertheless, revascularization has been attempted during the acute phase of myocardial infarction with the aim of preventing or minimizing permanent myocardial damage in the immediate postinfarct setting for recurrent ischemic pain, and during cardiogenic shock for the purpose of improving hemodynamic function.(27, 277, 13, 275, 51, 52)

In 1975, Berg, et. al. described 96 patients with acute myocardial infarction who underwent emergency cardiac catheterization and myocardial revascularization within an average of six hours from the onset of pain. The small increases observed in serum glutamic oxaloacetic transaminase levels preoperatively and postoperatively may be interpreted either to support these investigators' contention that myocardial necrosis was prevented by revascularization surgery, or to reflect the selection of patients with small myocardial infarctions for surgery.(277) There were five operative deaths and one late death in a follow-up of nearly four years.

It has recently been reported that operative mortality for ACBG, even in the setting of an acute myocardial infarction, can be gratifyingly low. As mentioned previously, Phillips, et. al. (27) reported an operative mortality of 1.6% for patients with evidence of an evolving myocardial infarction who were taken to the operating room within 6.5 hours of the onset of pain. Studies of this type demonstrate that "it can be done," however, it has yet to be proven that "it should be done." Unless such a study is carefully designed, its outcome can be severely biased by patient selection and other features.(25) The logistical problems of treating acute myocardial infarction with immediate surgery are formidable, if not insurmountable, in most centers. Unless distinct and compelling advantages for surgical revascularization are demonstrated, standard medical management is likely to prevail for the treatment of the evolving, uncomplicated myocardial infarction.

Levine, et. al. described 33 patients who were managed in the early recovery phase of a transmural myocardial infarct with intra-aortic balloon pumping and myocardial revascularization for angina resistant to intensive drug therapy.(254) Thirty patients survived ACBG with only one showing new Q waves in postoperative electrocardiograms. With an average follow-up of 38 months, the incidence of late death was less than 5%, and most patients were described as being fully active and without significant angina.

Leinbach, et. al. reported a series of 80 patients treated with the intra-aortic balloon pump for cardiogenic shock secondary to myocardial infarction.(51) Selective coronary and left ventricular cineangiography were performed in 52 balloon-dependent patients in this group. Of these, 22 were found to be inoperable and died; six who were found to be operable but did not have surgery also died. The remaining 24 patients underwent

ACBG in asociation with infarctectomy and mechanical repairs when indicated. There were only nine survivors (for an unspecified follow-up period). Johnson, et. al. concluded that functional recovery after surgery for cardiogenic shock depended not only on the extent of the infarction and on the coronary anatomy, but also on the ability to perform surgery within 12 hours of infarction or to support the patient with mechanical means for 10 to 14 days before performing surgery.(54)

A2though nonsurgical management of cardiogenic shock is almost universally unsuccessful in preventing death, the results of surgery have not produced a strong basis to support its widespread application in this setting. The limiting factor may continue to be the extent of irreversible myocardial damage causing cardiogenic shock. In a postmortem study, Page, et. al. found that the amount of left ventricular myocardium destroyed by recent and old infarcts in patients with acute myocardial infarction exceeded 40% in all 20 patients diagnosed as having cardiogenic shock, whereas only 1 of 14 without shock had lost that much myocardium.(278) If surgery is to be successful in the management of such patients, more than the efforts of the "occasional" surgeon and supporting team will be required. Therefore, the application of the procedure for this purpose will be limited.

The Role of ACBG in Patients with Associated Valve Disease

The combination of valve replacement and ACBG occurs in two distinctly different clinical settings, i.e., aortic and mitral valve disease. A high proportion of patients with angina and aortic stenosis of hemodynamic significance have been found to have coronary occlusive lesions.(279) Bonchek, et. al. found no significant coronary heart disease in 53 patients among 100 with aortic valve disease and the absence of angina, whereas Loop, et. al. found that only 18% of 80 consecutive patients requiring simultaneous aortic valve replacement and ACBG at the Cleveland Clinic had not experienced angina.(280, 55) Operative mortality was quite high in early reports, but it has approached that of valve replacement alone in more recent studies; the incidence reported for postoperative myocardial infarction has been 10 to 20%.(55, 281, 282) The rationale for combining ACBG with aortic valve replacement is based on the finding, in retrospective studies, that myocardial infarction secondary to coronary heart disease was a frequent cause of operative mortality in patients undergoing aortic valve replacement.(56)

Associated findings complicate assessment of the combination of mitral valve replacement with ACBG. Some maintain that the clinical course of hemodynamically significant mitral regurgitation, representing a terminal phase of diffuse coronary heart disease or occurring in the setting of recent myocardial infarction, is not significantly altered by the addition of ACBG to valve replacement.(282) On the other hand, Gann, et. al. concluded that surgery should not be denied to patients with medically unresponsive congestive heart failure secondary to papillary muscle dysfunction and coronary heart disease.(56) They reported 95% survival and postoperative improvement in the combined surgical procedure, regardless of the severity of coronary artery obstruction, as long as the cardiac index was at least 1.5 liter/min/m^2, the ejection fraction was at least 0.40, and all obstructed lesions were bypassed. Kay, et. al. advocate valvular repair rather than prosthetic valve replacement for mitral regurgitation resulting from coronary heart disease.(283) They reported that in a series of 45 patients, the combined valvular and revascularization procedure was associated with an operative mortality of only 7%, symptomatic improvement in all but 1 of 36 long-term survivors, and an actuarial survival rate of 80% at five years.

Information on combined valvular and revascularization procedures is likely to remain sporadic, as such interventions are not well suited to controlled study. Clinical circumstances are likely to be desperate when such surgery is contemplated, particularly in the case of mitral valve dysfunction. Complete hemodynamic studies with selective coronary arteriography should be performed when valve replacement is considered, and surgical steps should be taken for whatever structural lesions might lend themselves to improvement. When combined valvular and myocardial revascularization procedures are contemplated, one of the lesions is likely to be critical and force the issue; the other by itself may not constitute a justification for surgery. Because the first surgical attempt is most likely to help the patient, and because postoperative recovery may demand the utmost in cardiac reserve, it seems prudent to deal with all significant lesions simultaneously. If, in fact, one or more of the lesions has not become symptomatic, considerable judgment will be necessary in deciding whether to correct it during the operation. It must be recognized, however, that such recommendations are based more on clinical impressions and judgment than on scientific fact. Little effort has been made to compare the long-term results in patients subjected to combined procedures with those carefully selected and matched concurrent controls who received more limited operations.

The Role of ACBG with Ventricular Aneurysmectomy

Information on the use of ACBG in managing coronary heart disease complicated by ventricular aneurysm is derived largely from individual case reports and small series.(53, 54, 208, 284-287) Kitamura, et. al. reported clinical improvement and reduction of the ejection fraction after bypass surgery in nine patients with the noncontractile portion of the left ventricle localized to an area of 12 to 40% of the internal surface of the left ventricle.(274) The noncontractile portion was excised in five patients and excluded in four. Excision or exclusion of dyskinetic portions of left ventricular myocardium reduces end-diastolic volume and thereby improves the ejection fraction, even if stroke volume changes little, for the end-diastolic volume is the "denominator" of the ejection fraction. Shaw, et. al. reported improved survival over a three-year period for 35 patients with uncontrolled congestive heart failure; resection of a ventricular aneurysm was carried out with concomitant ACBG in 17.(285) Okies, et. al. found that 74% of 33 patients who had bypass grafting and aneurysmectomy were asymptomatic after three years, compared with only 53% of 24 patients who underwent only aneurysectomy.(53) Actuarial survival was nearly identical for the two groups; overall operative mortality was 10.5%. Aranda, et. al. described 18 patients who underwent ACBG and ventricular aneurysmectomy; the primary indications were intractable angina in seven of the patients, refractory congestive heart failure in nine, and recurrent ventricular tachycardia resistent to medical therapy in two.(286) Most of these patients had significant obstructive lesions in more than one coronary artery. Two patients died during surgery and one of the two who underwent surgery because of recurrent ventricular tachycardia died suddenly five months after surgery. Five of the 15 survivors continued to have congestive heart failure and angina on minimal effort. Only one became asymptomatic.

Crosby, et. al. recently published the follow-up of 66 patients who underwent ventricular aneurysmectomy and coronary revascularization between August, 1973, and June, 1978.(288) There were five hospital deaths (7.6%) and a 40 month acturial survival of 74%. These investigators pointed out that the proportion of patients fully employed increased from 33% preoperatively to 63% postoperatively, and total disability decreased from 60% preoperatively to 29% postoperatively. Their analysis of the financial implications for the community showed that the cost of surgery averaged $10,537 per patient. "Computing the income actually earned by the entire group of

patients, the disability payments to the individual patients and the loss of tax revenue from disability showed that the cost of surgery for the whole group could be paid back by 1.6 years of improved postoperative productivity."

Reoperation

ACBG may be unique among common surgical procedures in the proportion of repeat operations that might eventually be necessary. It is generally accepted that ACBG is basically a palliative procedure and does not retard the underlying disease process for which it is used. As noted earlier in this review, it even seems to accelerate the underlying pathology, especially with respect to the atherosclerotic occlusive process in the native circulation proximal to the graft. In addition, it may cause myocardial infarction perioperatively.

Early reports of ACBG done a second time in patients with clinical relapse discussed the technical problems.(289-296) In some of the patients, the initial procedure had incorporated internal mammary artery implantation or other methods of revascularization. Stiles, et. al. reported six deaths in 49 patients undergoing repeat coronary operations.(295) In addition, five functioning grafts from previous surgery were damaged and two ventricles were lacerated. In nine patients, the repeat procedure was less complete than planned because angiographically demonstrated targets could not be found. It can be anticipated that these results, reflecting early experience with a heterogenous group of patients, can be improved. But regardless of the nature of the first procedure and the experience of the surgical team, the results do not equal those expected from a first procedure by today's standards.(289-292) Winkle, et. al. analyzed the experience at Stanford in 21 reoperated patients.(290) Improvement was complete in seven instances, incomplete in six, and nonexistent in eight. Those patients whose symptoms were completely relieved by the second procedure had demonstrated new critical lesions or previously unbypassed critical lesions. It should be noted, however, that four of the seven patients having no angina after reoperation sustained perioperative infarctions. Reoperation was less successful in relieving angina when performed on patients with graft occlusion and in those with stable rather than unstable angina.

The experience in Nashville was similar for 31 patients who underwent reoperation for failure of one or more aortocoronary bypass grafts.(291) Of 24 patients followed for more than six months after the second procedure, only 15 (62%) clearly benefited, 3 had few symptoms but sustained myocardial infarctions, and 6 continued to have very significant symptoms. The Texas Heart Institute reported 41 patients among the 5,507 who undersent ACBG between 1969 and 1974 who had recurrent angina and received reoperation.(292) Follow-up information was obtained in 38 patients at a mean of 22 months. Angina was completely relieved in only 11 patients (28.8%), improved in 13 (34.2%), unchanged in 9 (23.6%) and worse in 5 (13.4%).

Norwood, et. al. reported that repeat revascularization was more likely to be successful if the original bypass was occluded and no evidence existed that arteriosclerosis had progressed.(296) In 26 patients undergoing a second surgical procedure for persistent or recurrent angina, most had one or more occluded grafts. Progression of atherosclerotic disease in ungrafted arteries was considered the sole cause of recurrent angina in only five patients. In the 12 patients without progression of arteriosclerosis, there was substantial benefit from the second revascularization procedure. In 6 of the 14 patients with evidence for progression of arteriosclerosis, the advance of the disease occurred in both previously grafted and ungrafted vessels; only two of this group were helped by the second bypass procedure.

The issue of reoperation can be expected to assume more importance as time passes, and angina has the opportunity to recur in large number of surgically treated patients. The increased technical difficulties, higher risks, and less satisfactory clinical responses associated with reoperation are compelling reasons to recomend ACBG only at the proper time for each individual patient. Coronary heart disease is a chronic disease and ACBG may be of less than optimal benefit if done prematurely (e.g., in the asymptomatic patient) or too late (e.g., only after irreversible damage has occurred).

Miscellaneous

There is growing literature on the role of ACBG as preliminary for surgery for stenosis of the carotid arteries and/or other great vessels. Demonstration of benefit is difficult. In most centers, such a plan requires two operations. In a few centers, however, both procedures are done as part of the same operation, with a seeming reduction in both morbidity and mortality.(297) Review of this important and expanding subject is beyond the scope of this manuscript.

EPILOGUE

There can be little doubt that more knowledge and experience regarding all aspects of coronary heart disease has been acquired in the past 12 years, since the first published report describing the operative technique of ACBG, than in the more than 300 years since Heberden described angina pectoris.(16) The ultimate role of ACBG in the management of coronary heart disease remains to be established. It is now generally agreed that ample evidence, both scientific and anecdotal, indicates that the greatest usefulness of the procedure is in the relief of angina pectoris refractory to acceptable medical management. If no other role were established, this one would be sufficient to establish the procedure as clinically useful and necessary. In addition, there is reasonable agreement that ACBG probably postpones death in many, if not most, symptomatic patients with significant obstruction of the left main coronary artery as well as patients with critical stenosis of the three major vessels, especially if associated with decreased ventricular performance. But after that, there is little general agreement. This is so because, for reasons not altogether clear, the natural history of the disease is changing. As Kloster stated, the problem may be that "it is unfortunate for those who set out to demonstrate improved survival with coronary artery bypass that current modes of medical management appear to have favorably altered the natural history of coronary artery disease."(162)

It is important that the physician always be mindful that what is recommended and seems effective today may not be recommended and effective next year, or a decade from now. It is important, too, in evaluating a specific therapy for a disease, to exercise great care to avoid introducing the preconceived biases of the investigator. Furthermore, the natural history of the disease may change, not only during the evolution of the therapy, but even after it was thought that a specific approach to therapy had been justified. The physician must always maintain an open mind and a high degree of skepticism. The history of anticoagulant therapy in the treatment of acute myocardial infarction illustrates this point.

Based on studies with heparin by Solandt, et. al. (298) in 1939 and the isolation of dicumarol that same year by Link, (299) Wright, et. al., (278) initiated in 1948 a major clinical trial to determine the effectiveness of anticoagulant therapy in the treatment

of acute myocardial infarction after receiving encouraging results from preliminary studies.(298,299, 278) It was one of the first, if not the first, such large-scale clinical trials ever completed. Twenty-three percent of the untreated patients and 16% of the treated patients died. Throughout the next two decades, individual physicians and investigators accepted or rejected the results of the study. However, it became apparent that the method of randomizing patients in that study was subject to bias. Patients admitted to cooperating hospitals on odd days were given anticoagulants and those admitted on even days were not. Thus, admitting physicians could predict the therapy to be used on any given day and select the day of admission for individual patients. Finally, in a more rigidly designed large-scale study, Hilden, et. al. in Denmark demonstrated that the mortality after the first 48 hours was 23% with and 25% without anticoagulant therapy.(301) The lack of effect was confirmed by another large-scale trial, planned with great care by the Medical Research Council of Great Britain and reported in 1969.(302)

Thus, it would appear at first glance, because of data from more critically designed studies, that Wright's observations were incorrect. Most clinicians therefore discarded the use of anticoagulants in the treatment of myocardial infarction. But not only was the experimental design changed from 1948 to 1963 to 1969, the natural history of the disease also changed. When Wright and his associates studied the effects of anticoagulants in the 1940s and early 1950s, the patient lay flat in bed. He did not feed himself; he was fed by a nurse, usually a private duty nurse. He did not use the toilet or a bedside commode, but rather was raised up so that a bed pan could be inserted in the proper position. Levin and Lown, realizing that cardiac output is less in the sitting than the supine subject, proposed the "chair" treatment; they recommended that two husky orderlies lift the patient from the bed to the chair.(5) Furthermore, the incidence of the shoulder-hand syndrome in the bedbound patient became significant.(303) In the first edition of Harrison's Principles of Internal Medicine, published in 1951 (the year Wright's clinical trial was nearly completed), only three and three-quarters pages were devoted to a discussion of myocardial infarction, and those pages were indexed only under the heading "angina pectoris."

By 1969, the time of the study of the Medical Research Council of Great Britain, Day (in 1963) had already reported preliminary studies on an acute coronary care area, and the 1965 Bethesda Conference Report on Training Techniques for Coronary Care Units had been published.(302, (304) Interns working in coronary care units had learned that the patient with an acute myocardial infarction would not "break" and so had the patient sit up in bed so that the lungs could be assessed more accurately for evidence of fluid retention. Nurses were in such short supply that the patient had to feed himself or starve. Thus, by 1969, the patient's likelihood of having a thromboembolic complication was much less than two decades before, when Wright and his colleagues initiated their study.

It is possible that the observations by Wright, Hilden, and the Medical Research Council of Great Britain all were accurately made and accurately interpreted.(300-302) All three reports may have been essentially correct, but the natural history of hospitalized patients with acute myocardial infarction had changed. The investigators were not looking at the same problem, although the name remained the same.

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